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ORIGINAL RESEARCH

# The long-term outcomes of a cohort of Sri Lankan patients with ulcerative colitis: a retrospective study at two national referral centers and review of literature

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Sudul Mananjala Senanayake[1]
Anthony Nilesh Ranjeev Fernandopulle[2]
Madunil Anuk Niriella[1,3]
Nethini Thilanga Wijesinghe[3]
Amanda Ranaweera[3]
Mohammadu Nisar Mufeena[3]
Arunasalam Pathmeswaran[4]
Nawarathnelage Meththananda Nawarathne[2]
Arjuna Priyadarsin de Silva[1,3]
Hithanadura Janaka de Silva[1,3]

[1]University Medical Unit, Colombo North Teaching Hospital, Ragama, Sri Lanka; [2]Gastroenterology Unit, National Hospital of Sri Lanka, Colombo, Sri Lanka; [3]Department of Medicine, Faculty of Medicine, University of Kelaniya, Ragama, Sri Lanka; [4]Department of Public Health, Faculty of Medicine, University of Kelaniya, Ragama, Sri Lanka

Correspondence: Hithanadura Janaka de Silva
Department of Medicine, Faculty of Medicine, University of Kelaniya, PO Box 6, Thalagolla Road, Ragama 11010, Sri Lanka
Tel +94 77 777 7862 (mobile); +94 11 295 3409
Fax +94 11 295 8337
Email hjanakadesilva@gmail.com

**Background:** Inflammatory bowel disease, especially ulcerative colitis, is increasing in many "non-Western" countries, including Sri Lanka. The aim was to evaluate long-term outcomes of ulcerative colitis in a Sri Lankan population.

**Methods:** A retrospective cohort study was conducted at the gastroenterology clinics of the Colombo North Teaching Hospital, Ragama and the National Hospital of Sri Lanka, Colombo; the two major referral centers for ulcerative colitis. All cases had histological confirmation of ulcerative colitis. Three outcomes: colectomy, development of colorectal carcinoma, and death were assessed. Patients not attending the clinic during the previous 4 weeks, or their families, were contacted to obtain clinical details and survival status. In those who had died, the cause of death was confirmed from clinical records and death certificates.

**Results:** Details of 348/425 (81.9%) patients with ulcerative colitis (mean age 45.6 [standard deviation {SD} 14.3] years, male/female ratio = 1.00:1.03) were available. The mean follow-up was 6.8 (SD 6.5) years. The cumulative colectomy rates at 1, 5, 10, and 15 years were 1.5%, 4.0%, 5.5%, and 9.3% respectively. The cumulative probability of colorectal cancer in this cohort after 10 and 15 years was 0.47% and 2.36% respectively. The cumulative survival rate after 1, 5, 10, and 15 years was 99.7%, 98.9%, 98.1%, and 94.5% respectively. Patients with pancolitis were more likely to have disease-related death ($P = 0.05$). Multivariate analysis (Cox proportional hazards model) showed that an older age at diagnosis was associated with long-term mortality (hazard ratio, 1.11; $P = 0.001$).

**Conclusion:** In this cohort, colectomy, colorectal carcinoma, and death rates were low, suggesting a relatively benign disease course for ulcerative colitis.

**Keywords:** survival, colectomy, colorectal carcinoma

## Introduction

Inflammatory bowel disease (IBD), especially ulcerative colitis (UC), is increasing in many "non-Western" countries including Sri Lanka. This is possibly related to changes in economic development, improved hygiene, and other changes in lifestyle.[1] The prevalence of UC in Sri Lanka was recently studied and found to be 5.3/100,000.[2] It has been suggested that differences in race and ethnicity among patients are associated with differences in disease phenotype and severity and that these differences may be related to the underlying genetic mutations.[3] In clinical practice, we have observed a milder disease course among our UC patients, compared with their "Western" counterparts, with an apparently low incidence of long-term complications.

The long-term outcome of UC has been well studied in Western populations[4,5] and more recently among East Asians.[6–9] However, such outcomes have been poorly studied in South Asian populations. We studied the long-term outcomes of a cohort of Sri Lankan patients with UC at two tertiary care hospitals, which are the main national referral centers for IBD.

## Material and methods

The study was conducted at the gastroenterology clinics of the University Medical Unit, Colombo North Teaching Hospital (CNTH), Ragama, and the National Hospital of Sri Lanka (NHSL), Colombo, the two main referral centers for IBD in Sri Lanka. Details of patients with IBD registered in these clinics had been maintained since their respective inceptions in 1995 and 2002.

### Study population

All patients diagnosed with UC were eligible for inclusion in the study. Patients with incomplete data, Crohn's disease, or those who had been categorized as IBD type unclassified were excluded. UC was diagnosed based on clinical, endoscopic, and histological findings. At both centers, the policy for surveillance of patients after diagnosis of UC for dysplasia and malignancy was in accordance with accepted current international guidelines, specifically those of the British Society of gastroenterology.[10]

### Study design

This was a retrospective cohort study. Clinical details of UC patients, including the date of diagnosis, were obtained from the combined database. Next, details of three long-term outcomes were sought; namely, colectomy, development of colorectal carcinoma (CRC), and death. Patients were first contacted at regular clinic visits. For those who had not attended the clinic within the previous 4 weeks, either the patient or their families were contacted by telephone or by post. Details of the outcomes and survival status were obtained. In cases where patients had died, details of death were ascertained. The cause of death was confirmed from death certificates and patient records. The Montreal classification of extent and severity of UC was adopted for this study.[11] The disease extent and severity, number of acute relapses, and presence of primary sclerosing cholangitis (PSC) were also assessed.

### Ethics approval

Prior ethics approval for this study was obtained from the Ethics Review Committee of the Faculty of Medicine, University of Kelaniya. Informed consent was taken from all participating patients and their families regarding obtaining information as well as follow-up data.

### Statistical analysis

Cumulative rates for colectomy, CRC, and death were calculated according to the "life table analysis" using Stata (StataCorp LP, College Station, TX, USA) version 8.2. A *P*-value of less than 0.05 was taken as statistically significant.

## Results

Details of 348/425 (81.9%) patients with UC (mean age 45.6 [standard deviation {SD} 14.3] years, male/female ratio = 1:1.03) were available for analysis. The mean age at disease onset was 45.6 (SD 14.3) years. Disease characteristics at presentation were: 31.9% had proctitis, 43% left-sided disease, and 25.1% pancolitis; 35.6% had severe, 38.8% moderate, and 25.6% mild disease. The median follow-up was 5.4 years (interquartile range 2.5–9.5 years). Among this cohort, a considerable number (43 [12.4%]) of patients had been referred recently and therefore had a follow-up of less than a year. However, 56 (16.1%) patients had a follow-up of over 10 years, and 10 (2.9%) of them a follow-up of over 20 years. During follow-up, 66.7% patients reported no relapse, 18% one relapse, and 19.3% two or more relapses. There were only 3 (0.86%) patients with PSC.

### Colectomy

Fifteen patients had undergone colectomy during follow-up. Among them, the majority (8/15) were performed during the first 2 years following diagnosis and only two carried out after 10 years following diagnosis. Two patients underwent colectomy due to acute severe UC (Table 1). The most common indication for colectomy was disease poorly controlled by medical therapy (8/15) (Table 1). Only two were performed after diagnosing CRC. Among patients who underwent colectomy, six had extensive disease, five had left-sided disease, and four had distal disease. The cumulative colectomy rates in

**Table 1** Indication for colectomy

| Indications for colectomy | Number |
|---|---|
| Acute ulcerative colitis/fulminate colitis | 2 |
| Colorectal carcinoma | 2 |
| Unresponsive to medical treatment; recurrent/ refractory disease | 8 |
| "Increased risk of cancer" | 2 |
| Suspected malignant stricture on Barium enema – found to be normal after surgery | 1 |
| Total | 15 |

this cohort at 1, 5, 10, and 15 years were 1.5%, 4.0%, 5.5%, and 9.3% respectively.

## Carcinoma

Only two patients were found to have CRC. One of them was diagnosed with pancolitis in 1995 and was diagnosed to have carcinoma of the transverse colon 10 years later on surveillance colonoscopy. The other had been diagnosed with UC (left-sided disease) in 1975 at the age of 23 years after presenting with a long-standing history of previously uninvestigated blood and mucus diarrhea, and was found to have a carcinoma of the descending colon at the initial sigmoidoscopy. She underwent colectomy soon afterwards and continues to be well more than 40 years after diagnosis. During the period of follow-up, no other patients in this cohort were found to have developed CRC. Since the only two patients found to have CRC had survived until the last date of contact, the survival rate among patients with UC with CRC in this cohort was 100%. Furthermore, the cumulative probability of CRC in this cohort after 10 and 15 years was 0.47% and 2.36% respectively.

## Deaths

Six patients had died during the period of follow-up (mean age 63.5 years). Two deaths were from causes clearly unrelated to UC (one due to a road traffic collision and the other an 85-year-old man who had a sudden death, possibly cardiac in origin) and were classified as "deaths unrelated to the disease." The other deaths were classified as "probable disease-related deaths" and compared with characteristics of the disease. Four patients had sepsis as the cause of death (although, one among them also had coexistent diabetes and cryptogenic cirrhosis). The patient who had cryptogenic cirrhosis had pancolitis and was on both sulfasalazine and azothiaprine when she developed sepsis. The other three who died of sepsis had died within 3 months of diagnosis. They had been treated with steroids. The cumulative survival rate after 1, 5, 10, and 15 years was 99.7%, 98.9%, 98.1%, and 94.5% respectively.

## Factors associated with long-term mortality

Multivariate analysis using the Cox proportional hazards model showed that an older age at diagnosis was associated with long-term mortality (hazard ratio, 1.11; $P = 0.001$). Patients with pancolitis were more likely to have disease-related death ($P = 0.05$) (after excluding "deaths unrelated to the disease"). Other than age at onset and disease extent, factors such as gender, disease duration, and presence of PSC were not associated with long-term mortality.

# Discussion

In this cohort of patients with UC from both the major referral centers for IBD in the country, colectomy rates, CRC, and deaths were low. The cumulative colectomy rates at 1, 5, 10, and 15 years were 1.5%, 4%, 5.5%, and 9.3% respectively. Previously, the cumulative colectomy rates in UC among "Western populations" had been found to be as high as 20%, 28%, and 45% at 5, 10, and 25 years.[12] More recent studies report lower rates, though they still remain relatively high at about 9.8% at 10 years[13] (Table 2), and overall, the rate is accepted to be about 1% per year.[14] A significant geographical variation in colectomy rates has been reported by Hoie et al in a study involving seven countries, with countries in Southern

**Table 2** Comparison of cumulative colectomy rates at different reported time internals in the "Western" and "Eastern" studies

| Study | 1 year | 3 years | 5 years | 10 years | 15 years | 25 years |
|---|---|---|---|---|---|---|
| Leijonmarck et al[12] | | | 20% | 28% | | 45% |
| Stockholm, Sweden | | | | | | |
| Solberg et al (IBSEN study)[13] | | | | 9.8% | | |
| Eastern Norway | | | | | | |
| Hoie et al[15] | | | | | | |
| Northern Europe | | | | 10.4% | | |
| Southern Europe | | | | 3.4% | | |
| Matsui et al[6] | | | | 16.5% | 38.5% | |
| Japanese population | | | | | | |
| Hilmi et al[7] | 3.4% | | 5.9% | 15.6% | | |
| Malaysia | | | | | | |
| Chow et al[9] | 2.4% | | | 7.6% | | |
| Hong Kong | | | | | | |
| Park et al[8] | 2.0% | 2.8% | 3.3% after 5–15 years | | | |
| South Korea | | | | | | |
| Our study | 1.5% | | 4.0% | 5.5% | 9.3% | |

**Abbreviation:** IBSEN, Inflammatory Bowel disease in South East Norway.

Europe having a rate of 3.4% at 10 years, significantly lower than their North European counterparts.[15] High rates have been reported from Japan, with a cumulative colectomy rate of 16.5% at 10 years and 38.5% at 15 years.[6] Hilmi et al reported that a multiracial population in Malaysia had overall cumulative colectomy rates of 3.4%, 5.9%, and 15.6% at 1, 5, and 10 years respectively.[7] Lower rates have been found in South Korea, where the cumulative probability of colectomy was 2% after 1 year, 2.8% after 3 years, and 3.3% after 5–15 years,[8] and in Hong Kong where cumulative colectomy rates reported in a Chinese population were 2.4% and 7.6% at 1 and 10 years.[9] The colectomy rates found in our population are at the lower end of the spectrum and similar to those reported in Southern European countries, South Korea, and Hong Kong (Table 2).

In our cohort of 348 patients, only two patients had CRC. One was an unusual case of a 23-year-old patient with uninvestigated blood and mucus diarrhea who was found to have CRC at the time of diagnosis of UC. Young age at onset of colitis has been described to increase the risk of CRC.[16] More importantly, only one patient had developed CRC during follow-up endoscopy. The cumulative probability of CRC in our patients was low: 0.47% after 10 years and 2.36% after 15 years. While the overall risk of developing CRC increased in patients with UC, the magnitude has been difficult to estimate.[17] In 2001 a meta-analysis based on "Western data" reported cumulative probabilities of CRC to be 2% by 10 years, 8% by 20 years, and 18% by 30 years,[18] and also reported a geographical variation among countries.[18] However, more recent reports suggest that the CRC risk has decreased over time.[19] Although controversy still exists, recent data suggest that the overall risk of CRC may be as low as 2% at 30 years.[20,21] Data from the Olmsted County database in the United States did not find any increased risk of CRC in UC over a 14 year follow-up.[20] Even among patients with extensive disease, although the cumulative risk of cancer may be 7%–15% at 20 years, the risk up to 15 years is considered low.[14] Reports from Asia also suggest a low CRC rate, with Chow et al reporting only one out of 172 patients[9] and Hilmi et al reporting no CRC among 118 patients from Malaysia.[7]

The cumulative survival rate in our cohort after 1, 5, 10, and 15 years was 99.7%, 98.9%, 98.1%, and 94.5% respectively, suggesting a low mortality rate. Although acute severe UC can be a life-threatening disease,[22] with a mortality rate of less than 2%,[14] most studies report the overall survival to be good and similar to that of the general population.[13,23–25] A similar survival is reported in Asian studies,[6,9] with Park et al reporting a cumulative survival rate after 1, 5, and 10 years of 100%, 99.4%, and 97.4% respectively in a South Korean population.[8]

Among the six deaths in our sample of 348, two were clearly not related to UC. Four other deaths in this cohort had been attributed to sepsis. Furthermore, one patient had the significant comorbidity of cryptogenic cirrhosis and diabetes. All these patients were known to have been on immunosuppressive treatment. The cause of death may be more directly attributable to complications of treatment or comorbidity rather than the disease itself. In the literature, about a fifth of deaths have been directly related to UC, mostly from colorectal cancer or postoperative complications.[25] This was not so in our population as there were no deaths due to toxic megacolon, CRC, or complications of surgery.

Mean age at diagnosis among the patients who died was 63.5 years, significantly higher than the overall mean age at diagnosis of the cohort (45.6 years). Multivariate analysis using the Cox proportional hazards model also showed that this older age at diagnosis was associated with long-term mortality (hazard ratio, 1.11; $P = 0.001$). Similarly, Winther et al in 2003 reported an increased mortality in older patients[26] in the first 2 years after diagnosis. However, Viscido et al reported a higher mortality in patients less than 30 years of age.[27] A recent review of the literature suggests that the age at diagnosis of UC does not affect the standard mortality ratios when compared with the general population.[25] Our finding of older UC patients having a higher mortality would also be compatible with comorbidity and causes unrelated to UC being a significant contributory factor for mortality. Patients with pancolitis were more likely to have "disease-related death." Disease extent is associated with mortality in UC,[26] although a meta-analysis found that the increased risk was mainly in the first years after diagnosis.[28]

The presence of PSC is associated with increased risk of carcinoma and mortality.[29] This was not seen in our study due to the small numbers of patients with PSC (3/348) as well as small numbers of carcinoma and deaths. Previous studies have reported a higher percentage of patients having pancolitis (36.7%)[30] than in our study (25.2%). The pattern of disease extent may at least partly explain the low rate of complications in our cohort.

The retrospective nature of this study is a major limitation. This is reflected by the fact that only 348 out of a population of 425 patients could be followed up; 18.1% had been lost to follow-up. This was mainly due to the changes in addresses and phone numbers of patients making it impossible for us to contact them.

Another significant limitation was that individual treatments patients received were not used for analysis in this study. In Sri Lanka, as in many developing countries, treatment details are not recorded and continuously updated on electronic data records. Therefore, details of individual treatments were not available for a considerable number of patients, and therefore were not analyzed. Furthermore, as many patients were contacted by phone, compliance with drug treatment could not be reliably verified. Therefore, it was decided to use only known definite endpoints such as colectomy, development of CRC, and death in assessing long-term outcomes.

However, despite these limitations, to the best of our knowledge, this is the first study to address the long-term outcome in UC patients in a South Asian population.

In conclusion, we report low rates of colectomy, CRC, and death in a cohort of Sri Lankan patients with UC, similar to patient populations in some Asian and Southern European countries.

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## Disclosure

The authors report no conflicts of interest in this work.

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