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Natural History of Elderly-onset Ulcerative Colitis: Results from a Territory-wide Inflammatory Bowel Disease Registry

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Abstract

Background and Aims: Data on the natural history of elderly-onset ulcerative colitis [UC] are limited. We aimed to investigate clinical features and outcomes of patients with elderly-onset UC.
Methods: Patients with a confirmed diagnosis of UC between 1981 and 2013, from 13 hospitals within a territory-wide Hong Kong Inflammatory Bowel Disease Registry, were included. Clinical features and outcomes of elderly-onset patients, defined as age ≥ 60 years at diagnosis, were compared with those of non-elderly-onset disease [< 60 years at diagnosis].
Results: We identified 1225 patients, of whom 12.8% [157/1225; 56.1% male] had elderly-onset UC. Median duration of follow-up was 11 years [interquartile range, 6–16 years]. Age-specific incidence of elderly-onset UC increased from 0.1 per 100 000 persons before 1991 to 1.3 per 100 000 persons after 2010. There were more ex-smokers [32.2% vs. 12.2%, $p < 0.001$] and higher proportion of comorbidities [$p < 0.001$] in elderly-onset than non-elderly-onset patients. Disease extent, corticosteroids, immunosuppressants use, and colectomy rates were similar between the two groups. Elderly-onset disease was an independent risk factor for cytomegalovirus infection [odds ratio 2.9, 95% confidence interval 1.6–5.2, $p < 0.001$]. More elderly-onset patients had *Clostridium*

difficile infection [11.0% vs. 5.4%, $p = 0.007$], hospitalisation for UC exacerbation [50.6% vs. 41.8%, $p = 0.037$], colorectal cancer [3.2% vs. 0.9%, $p = 0.033$], all-cause mortality [7.0% vs. 1.0%, $p < 0.001$], and UC-related mortality [1.9% vs. 0.2%, $p = 0.017$] than non-elderly-onset patients.
Conclusions: Elderly-onset UC patients are increasing in number. These patients have higher risk of opportunistic infections, hospitalisation, colorectal cancer, and mortality than non-elderly-onset patients. Management and therapeutic strategies in this special group need careful attention.

Key Words: Natural history; elderly-onset; ulcerative colitis

1. Introduction

Ulcerative colitis [UC] is an idiopathic, chronic inflammatory disorder of the colonic mucosa, which results from a combination of genetic predisposition, environmental factors, and abnormal immune responses to the gut microbiota.[1,2] The incidence of UC is increasing over time around the world, including in traditionally low-prevalence regions such as Asia, Eastern Europe, and the Middle East.[3] The rise in incidence has been reported across all age groups, including early childhood, and is based on recent data also in the elderly population.[4] In most of the developing countries, UC remains the predominant disease when compared with Crohn's disease. With the ageing of the population, the incidence of elderly-onset UC is expected to increase.[4,5,6]

Studies have suggested that the phenotype and natural history of the disease may differ according to the age of disease onset.[4] As most severe episodes occur during the first few years of disease onset, and the patient's ability to tolerate underlying disease activity diminish with ageing,[7,8] elderly-onset patients should be treated differently from elderly patients with the disease starting at a younger age. Elderly UC patients may suffer from comorbidities and polypharmacy,[5,9] which could be associated with worse disease outcomes,[10] drug-drug interactions,[11] and complications after surgery.[5,12,3,14,15,16]

There are currently limited data on the characteristics, disease course, and treatment impact in elderly-onset inflammatory bowel disease [IBD] patients. In most studies, elderly-onset IBD was not clearly distinguished from elderly patients with disease starting at a younger age. In addition, few studies of unselected cohorts have focused on impact of age on prognosis including surgery, cancer, and mortality.[8,17,18,19,20] A better knowledge of the disease features and clinical outcomes of this unique population is essential to optimise management. In this study, we aimed to investigate the clinical features and disease outcomes of Chinese patients with elderly-onset UC compared with non-elderly-onset UC, using a territory-wide IBD registry.

2. Methods

We identified UC patients diagnosed between 1981 and 2013 within the Nixon-TAM Hong Kong IBD Registry. This represents the first territory-wide IBD registry in a Chinese population, which was established in 2013. This registry includes retrospective and prospective data collection of patients with IBD across 13 major public hospitals in Hong Kong. Hong Kong has a population of 7.2 million, and the majority of patients with chronic disease such as IBD seek public healthcare and follow-up in these 13 hospitals. More than 95% of all IBD patients in Hong Kong have been served by these study centres for the past 25 years. The healthcare system in Hong Kong has not changed substantially during the past two decades. The medical healthcare in Hong Kong is largely managed by the Hospital Authority which is a statutory body established in 1990 to manage all public hospitals and institutions in Hong Kong. It provides a comprehensive range of secondary and tertiary specialist care to all Hong Kong citizens, and all individuals have equal access to healthcare. The diagnosis of UC was confirmed according to the Lennard-Jones criteria based on clinical symptoms, endoscopy, and histology.[21] All cases were re-evaluated by one independent investigator [HYS] for this study using the above criteria. We only included confirmed UC patients, who had been followed up for ≥ 2 years, and who were followed up for at least once per year after 2011. For the purpose of this study, patients with elderly-onset UC were defined as patients aged ≥ 60 years at diagnosis, whereas those who were < 60 years of age at diagnosis were regarded as non-elderly-onset patients. We set 60 years old as the cut-off age for elderly-onset and non-elderly-onset to be consistent with previous population-based studies.[17,20] Clinical features and disease course were compared between the two groups.

2.1. Data collection

Data were extracted from patient electronic files into standardised questionnaires specifically designed for the registry. All records were reviewed for completeness and accuracy by physicians treating the patients. Data were entered into the registry database independently by two research staff. Age, gender, smoking status [current smokers were defined as subjects who still smoked, ex-smokers were defined as those who had stopped smoking, and non-smokers were patients who had never smoked, at the time of UC diagnosis], family history of IBD among the first-degree relatives, comorbidities, year of symptom onset and UC diagnosis, disease extent [according to the Montreal classification[22]: proctitis was defined as a proximal extent of inflammation distal to the retrosigmoid junction; left-sided colitis was defined as limited to the colorectum distal to the splenic flexure; extensive colitis was defined as extending proximally to the splenic flexure], episodes of severe colitis [defined as bloody stool frequency ≥ 6/day, or heart rate > 90 bpm, or temperature > 37.8 °C, or haemoglobin < 10.5 g/dl, or erythrocyte sedimentation rate > 30 mm/h, or C-reactive protein > 30 mg/l,[23]] hospitalisation for UC exacerbation, and medications were recorded. Steroid dependency was defined as either the inability to reduce steroids below the equivalent of prednisolone 10 mg/day within 3 months of starting steroids, or a relapse within 3 months of stopping steroids; and steroid refractory was applied to patients who had active disease despite increasing prednisolone to 0.75 mg/kg/day over a period of 4 weeks.[24] Cytomegalovirus [CMV] or *Clostridium difficile* [*C. difficile*] infections during follow-up, colectomy, and mortality were recorded. CMV infection was defined by haematoxylin and eosin stain together with immunohistochemistry. *C. difficile* infection was determined if one of the following tests had a positive result: stool *C. difficile* A & B enzyme immunoassay for *C. difficile* toxin, gene polymerase chain reaction [PCR], or stool culture. Death that occurred during UC flares or caused by complications of UC was regarded as associated with UC. Colonoscopy and histology records were reviewed for diagnosis

of dysplasia [ie adenoma-associated dysplasia, flat dysplasia] and colorectal cancer [CRC]. Dysplasia was classified as low-grade dysplasia [LGD] or high-grade dysplasia [HGD].[25]

2.2. Statistical analysis

Age-specific incidence was defined as age-specific incident cases/age-specific Hong Kong population per 100 000 persons in the corresponding year. Standardised mortality ratio [SMR, = observed/expected number of deaths] for overall mortality and standardised incidence ratio [SIR, = observed/expected number of incident cases] for CRC with 95% confidence interval [CI] were calculated. Expected deaths and incident CRC cases were estimated on the basis of age-sex specific mortality rate [data source: http://www.censtatd.gov.hk/home/] and CRC incidence rate [data source: http://www3.ha.org.hk/cancereg/e_a1b.asp] of the background population in Hong Kong, respectively; 95% CIs were calculated based on the assumption of a Poisson distribution for deaths and incident CRC cases. Categorical variables were analysed using chi-square test or Fisher's exact test. Continuous variables were analysed using the t-test if they were normally distributed or Mann-Whitney U test if there was a skewed distribution. Variables which were found to meet statistical significance associated with CMV and *C. difficile* infections, hospitalisation, and UC-related mortality in univariate analysis were assessed in multivariate analysis using backward stepwise logistic regression [variables with probabilities > 0.1 were removed in stepwise]. Cumulative probabilities of colectomy and flat dysplasia were analysed by Kaplan-Meier analysis and log-rank test. Two-sided p values < 0.05 were considered significant. Statistical analyses were performed with IBM SPSS Statistics 20.0.

2.3. Ethical considerations

The study was approved by the ethics committee of each participating centre.

3. Results

3.1. Patient characteristics

Within our registry, 1328 patients were screened and 1225 were included in this study; 20 [1.5%] of patients were excluded as follow-up was less than 2 years; 54 [4%] patients were lost to follow-up; and 29 [2%] patients were excluded due to lack of histological confirmation. Median time from symptom onset to disease diagnosis was 7 months (interquartile range [IQR], 2–20 months]. After diagnosis, patients were followed up regularly. Median duration of follow-up was 11 years [IQR, 6–16]; 157 patients [12.8%] had elderly-onset disease. Mean age at UC diagnosis increased from 33.64 (standard deviation [SD] 11.59] years old before 1990 to 46.58 [SD 15.82] after 2010 [Figure 1]. Age-specific incidence of elderly-onset UC increased from 0.1 per 100 000 persons before 1991 to 1.3 per 100 000 persons after 2010 [Figure 2]. The proportion of newly diagnosed elderly-onset UC has increased significantly during the past two decades [from 3.0% before 1990 to 21.6% after 2010, $p < 0.001$, Figure 3].

Among elderly-onset patients, the proportion of ex-smokers [32.2%] was significantly higher than that of non-elderly-onset patients [12.2%, $p < 0.001$], Elderly-onset patients and 1.7% had a family history of IBD among first-degree relatives. The corresponding proportion was 2.5% among non-elderly-onset patients. The proportions of comorbidities, including cerebrovascular accidents, hypertension, ischaemic heart disease, chronic obstructive pulmonary disease [COPD], diabetes mellitus, renal insufficiency, and extra-intestinal malignancy were significantly higher among elderly-onset patients [$p < 0.001$]. Extent of UC was similar in both groups at diagnosis, with an even distribution among proctitis, left-sided colitis, and extensive colitis [Table 1]. Of elderly-onset patients with proctitis at diagnosis, 9.0% progressed to left-sided colitis [$n = 14$] and 11.6% progressed to extensive colitis [$n = 18$] at maximal follow-up, and among patients with left-sided colitis at diagnosis, 12.9% progressed to extensive colitis [$n = 20$]. For non-elderly-onset patients, the corresponding proportions were 8.4% [$n = 89$], 5.5% [$n = 58$], and 10.8% [$n = 114$]. Altogether, UC location progressed in 33.5% of elderly-onset patients and in 24.6% of non-elderly-onset patients [$p = 0.018$]. Significantly more elderly-onset patients progressed from proctitis to extensive colitis [$p = 0.003$] [Figure 4].

3.2. Clinical outcomes of elderly-onset UC

3.2.1. Disease severity and therapy

Nearly one-quarter [24.7%] of elderly-onset patients had experienced severe UC attacks, and the majority of severe attacks occurred within the first few years after disease diagnosis. Similar to patients with non-elderly-onset disease, systemic steroids use was frequent [52.9%] and steroid dependency or refractory disease was common [40.7% of patients who had used systemic steroids] among

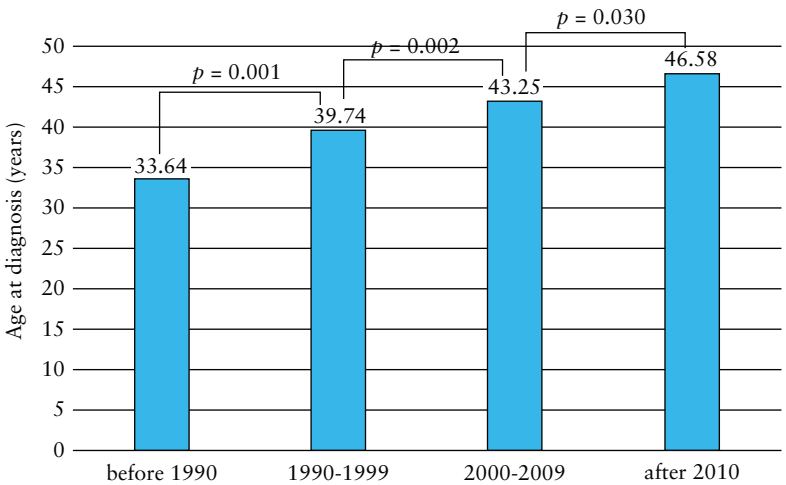

Figure 1. Age at ulcerative colitis [UC] diagnosis increased over time.

elderly-onset patients. Immunosuppressants use also did not differ between the two groups [27.3% of elderly-onset vs. 29.2% of non-elderly-onset, $p = 0.630$]. None of the elderly-onset patients had used biologicsal, whereas 2.1% of non-elderly-onset patients had used biologicals. Colectomy rates were not different between elderly-onset and non-elderly-onset patients [5.2% vs. 4.9%, $p = 0.875$]. Four [2.5%] elderly-onset patients and 17 [1.6%] non-elderly-onset patients had emergency colectomies for acute severe UC [$p = 0.333$]. There was no significant difference of scheduled colectomies for chronic active disease, neoplasia, or CRC between the two groups [$p = 0.629$] [Table 2]. Cumulative probabilities of colectomy were 6.1% at 10 years and at up to 20 years of follow-up in elderly-onset patients, compared with 3.7% at 10 years and 6.8% at 20 years of follow-up in non-elderly-onset patients [$p = 0.446$].

3.3. Disease complications

CMV [11.7% vs. 4.2%, $p < 0.001$] and *C. difficile* infections [11.0% vs. 5.4%, $p = 0.007$] were significantly more prevalent among elderly-onset than non-elderly-onset patients during the course of disease.

In univariate analysis, having an elderly-onset disease (odds ratio [OR] 3.0, 95% confidence interval [CI] 1.7–5.4, $p < 0.001$) and extensive colitis [OR 10.0, 95% CI 2.4–41.5, $p = 0.001$] were associated with CMV infection. In multivariate analysis, both of the two variables retained significance: elderly-onset [OR 2.9, 95% CI 1.6–5.2, $p < 0.001$], extensive colitis [OR 9.5, 95% CI 2.3–39.4, $p = 0.002$].

In univariate analysis, elderly-onset [OR 2.2, 95% CI 1.2–3.8, $p = 0.008$], left-sided colitis [OR 6.9, 95% CI 1.6–29.6, $p = 0.009$], extensive colitis [OR 9.6, 95% CI 2.3–39.9, $p = 0.002$], COPD [OR 4.9, 95% CI 1.6–15.4, $p = 0.007$], and liver cirrhosis [OR 6.8, 95% CI 1.7–26.8, $p = 0.006$] were associated with *C. difficile* infection. In multivariate analysis, the independently associated factors were: left-sided colitis [OR 6.9, 95% CI 1.6–29.8, $p = 0.009$], extensive colitis [OR 9.2, 95% CI 2.2–38.4, $p = 0.002$], COPD [OR 4.9 95% CI 1.5–15.7, $p = 0.008$], and liver cirrhosis [OR 6.0, 95% CI 1.5–24.7, $p = 0.012$].

Significantly more elderly-onset patients had hospitalisation for UC exacerbation than non-elderly-onset patients [50.6% vs. 41.8%, $p = 0.037$]. In univariate analysis, elderly-onset [OR 1.4, 95% CI 1.0–2.0, $p = 0.038$], left-sided colitis [OR 4.1, 95% CI 2.7–6.4, $p < 0.001$], extensive colitis [OR 7.5, 95% CI 5.0–11.3, $p < 0.001$], CMV infection [OR 9.5, 95% CI 4.2–21.2, $p < 0.001$], *C. difficile* infection [OR 25.7, 95% CI 6.2–107.1, $p < 0.001$], heart disease [OR 1.6, 95% CI 1.0–2.5, $p = 0.045$] and renal insufficiency [OR 2.1, 95% CI 1.0–4.2, $p = 0.041$] were associated with admission. Multivariate analysis showed left-sided disease [OR 4.0, 95% CI 2.6–6.1, $p < 0.001$], extensive colitis [OR 6.4, 95% CI 4.2–9.7, $p < 0.001$], CMV infection [OR 7.4, 95% CI 3.2–17.0, $p < 0.001$], and *C. difficile* infection [OR 18.5, 95% CI 4.4–77.7, $p < 0.001$] were independently associated with hospitalisation for UC exacerbation.

Eleven deaths were observed in each group, with the proportions of mortality as 7% and 1% in elderly-onset and non-elderly-onset patients, respectively. Although all-cause mortality was lower than expected in elderly-onset patients [SMR 0.5, 95% CI 0.3–0.9], the proportion of UC-related mortality was significantly higher in patients with elderly-onset disease [1.9% vs. 0.2%, $p = 0.017$]. Three elderly-onset deaths were related to the disease as follows: during an intractable severe flare within the first year of UC diagnosis, $n = 1$; severe sepsis during a UC flare, $n = 1$; severe sepsis after an operation for UC, $n = 1$. Two non-elderly-onset deaths were associated with UC as follows: fulminant pneumonia related to long-term steroid use and pancytopenia after azathioprine [AZA], $n = 1$; CRC with

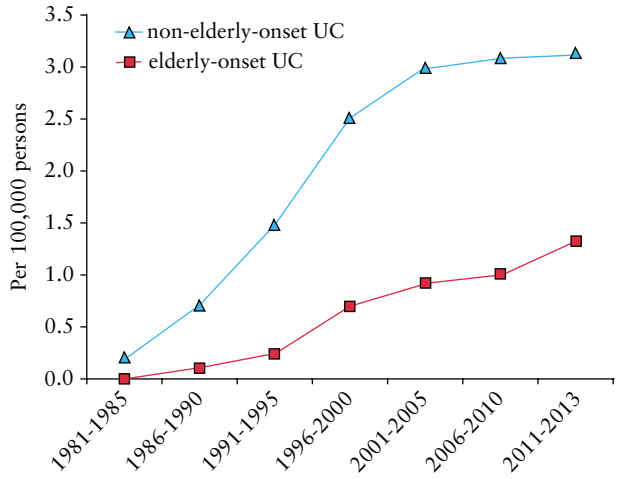

Figure 2. Age-specific incidence of elderly-onset ulcerative colitis [UC].

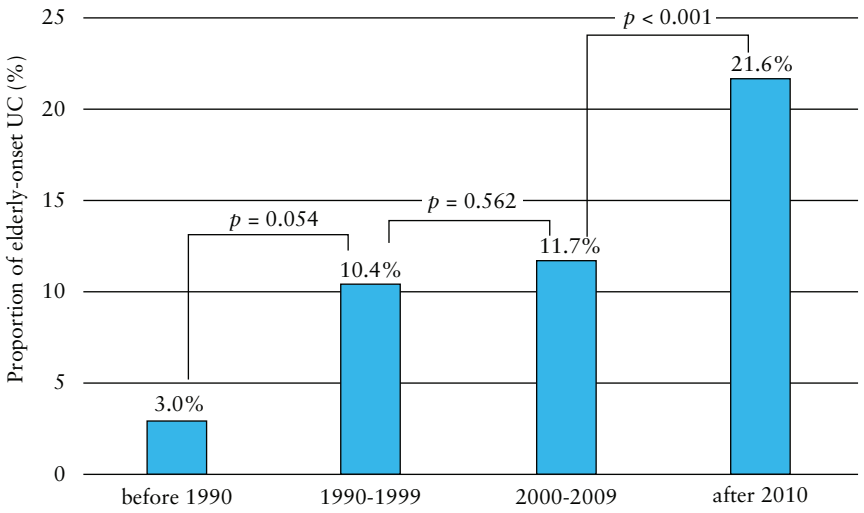

Figure 3. Proportion of incident elderly-onset ulcerative colitis [UC] increased over time.

Table 1. Patient characteristics.

	All patients [*n* = 1225]	Elderly-onset [*n* = 157]	Non-elderly-onset [*n* = 1068]	*p*-Value*
Age at diagnosis (median [IQR]) [years]	41 [31–52]	66 [63–72]	39 [30–48]	-
Male [*n*, %]	687 [56.1]	95 [60.5]	592 [55.4]	0.231
Duration from disease onset to diagnosis (median [IQR]) [months]	7 [2–20]	7 [2–22]	7 [2–18]	0.739
UC duration (median [IQR]) [years]	11 [6–16]	8 [4–14]	11 [6–16]	< 0.001
UC extent [at diagnosis]				0.623
Proctitis [*n*, %]	402 [32.8]	53 [33.8]	349 [32.7]	
Left-sided colitis [*n*, %]	400 [32.6]	54 [34.4]	346 [32.4]	
Extensive colitis [*n*, %]	404 [33.0]	46 [29.3]	358 [33.5]	
Missing data [*n*, %]	19 [1.6]	4 [2.5]	15 [1.4]	
UC extent [ever worst]				0.334
Proctitis [*n*, %]	223 [18.2]	22 [14.0]	201 [18.9]	
Left-sided colitis [*n*, %]	376 [30.8]	50 [31.8]	326 [30.6]	
Extensive colitis [*n*, %]	623 [51.0]	85 [54.1]	538 [50.5]	
Smoking status at diagnosis				
Current smoker [*n*, %]	106 [8.6]	12 [7.6]	94 [8.8]	0.589
Ex-smoker [*n*, %]	163 [13.3]	46 [29.3]	117 [11.0]	< 0.001
Non-smoker [*n*, %]	831 [67.8]	85 [54.1]	746 [69.8]	< 0.001
Missing data [*n*, %]	125 [10.2]	14 [8.9]	111 [10.4]	
Family history of IBD among first-degree relatives [*n*, %]	25 [2.4]	2 [1.7]	23 [2.5]	0.759
Comorbidity				
Cerebrovascular disease [*n*, %]	44 [3.6]	22 [14.0]	22 [2.1]	< 0.001
Hypertension [*n*, %]	248 [20.2]	86 [54.8]	162 [15.2]	< 0.001
Heart disease [*n*, %]	81 [6.6]	28 [17.8]	53 [5.0]	< 0.001
Chronic obstructive pulmonary disease [*n*, %]	18 [1.5]	14 [8.9]	4 [0.4]	< 0.001
Diabetes [*n*, %]	96 [7.8]	25 [15.9]	71 [6.6]	< 0.001
Renal insufficiency [*n*, %]	34 [2.8]	13 [8.3]	21 [2.0]	< 0.001
Cirrhosis [*n*, %]	10 [0.8]	3 [1.9]	7 [0.7]	0.126
Extraintestinal malignancy [*n*, %]	50 [4.1]	15 [9.6]	35 [3.3]	< 0.001

IQR, interquartile range; IBD, inflammatory bowel disease; UC, ulcerative colitis,
*Elderly-onset vs. non-elderly-onset patients.

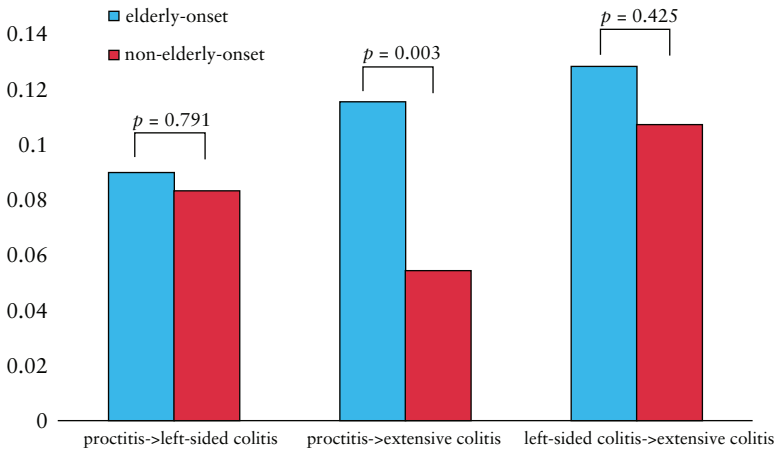

Figure 4. Progress of ulcerative colitis [UC] extent.

multiple metastases, *n* = 1. In multivariate analysis, only cerebrovascular disease [OR 7.1, 95% CI 1.0–49.3, *p* = 0.046] and ischaemic heart disease [OR 11.4, 95% CI 1.7–75.4, *p* = 0.012] were independently associated with UC-related mortality [Table 3].

3.4. Dysplasia and colorectal cancer

The absolute proportions for CRC were 3.2% and 0.9% in elderly-onset and non-elderly-onset patients, respectively [*p* = 0.033]. The incidence rates of CRC in elderly-onset and non-elderly-onset UC were 3.541 and 0.705 per 1000 person-years, respectively, with adjustment for colectomy. The observed number of incident CRC cases among elderly-onset UC patients was not significantly different from in the general population [SIR 0.4, 95% CI 0.0–2.4]. Elderly-onset patients were more likely to have adenoma [28.6% vs. 12.0%, *p* < 0.001] and adenoma-related HGD or CRC [3.2% vs. 0.8%, *p* = 0.017]. The proportions of flat dysplasia were not significantly different between the two groups [5.8% in elderly-onset and 8.2% in non-elderly-onset, *p* = 0.319].

In non-elderly-onset patients, the median duration of UC at the time of flat dysplasia was 8 years [IQR 3–13 years]. The rate of flat dysplasia was significantly higher in patients having ≥ 8 years of disease duration compared with those having < 8 years of disease duration [11.0% vs. 2.9%, $p < 0.001$]. Cumulative probabilities of flat dysplasia were 1.2% at 1 year, 3.6% at 5 years, 6.4% at 10 years, and 12.8% at 20 years of follow-up.

Among elderly-onset patients with flat dysplasia, 44% [4 out of 9] had flat dysplasia during the first year of UC diagnosis. The median duration of UC at the time of flat dysplasia was 1 year [IQR 0–13 years]. The rate of flat dysplasia was not different between patients with disease duration ≥ 8 years and those with < 8 years of disease duration [6.2% vs. 5.5%, $p = 1.000$, Table 5]. Cumulative probabilities of flat dysplasia were 3.2% at 1 year, 4.2% from 5–10 years, and 11.4% at 20 years of follow-up [compared with those in non-elderly-onset patients, $p = 0.754$].

4. Discussion

In our study, elderly-onset UC increased significantly over the past two decades. To our knowledge, this is the first territory-wide study showing that elderly-onset UC patients have higher risks of UC extent progression, CMV and *C. difficile* infections, hospitalisation, and UC-related mortality than non -elderly-onset patients, and more

Table 2. Disease outcomes of elderly-onset and non-elderly-onset UC.

	Elderly-onset [*n* = 157]	Non-elderly-onset [*n* = 1068]	*p*-Value
Severe colitis ever had [*n*, %]	38 [24.7]	211 [20.0]	0.184
Duration from diagnosis to severe attack (median [IQR]) [years]	1 [0–3.75]	1 [0–6]	0.258
Systemic steroids used [*n*, %]	81 [52.9]	525 [50.1]	0.511
Steroid dependent/refractory [*n*, % of patients used steroids]	33 [40.7]	246 [47.1]	0.284
Immunosuppressants used [*n*, %]	42 [27.3]	307 [29.2]	0.630
Biologicals used [*n*, %]	0	22 [2.1]	0.100
Colectomy [*n*, %]	8 [5.2]	52 [4.9]	0.875
Acute colectomy [*n*, %]	4 [2.5]	17 [1.6]	0.333
Scheduled colectomy [*n*, %]	6 [3.8]	33 [3.1]	0.629
CMV infection [*n*, %]	18 [11.7]	44 [4.2]	< 0.001
CDI [*n*, %]	17 [11.0]	57 [5.4]	0.007
Hospitalisation for UC exacerbation [*n*, %]	78 [50.6]	441 [41.8]	0.037
Mortality [*n*, %]	11 [7.0]	11 [1.0]	< 0.001
SMR [95% CI]	0.5 [0.3–0.9]	0.8 [0.5–1.4]	
UC-related mortality [*n*, %]	3 [1.9]	2 [0.2]	0.017

UC, ulcerative colitis; IQR, interquartile range; CMV, cytomegalovirus; CDI, *Clostridium difficile* infection; SMR, standardised mortality ratio; CI, confidence interval.

Table 3. Univariate and multivariate analysis for associated factors.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
CMV infection						
Elderly-onset	3.0	1.7–5.4	< 0.001	2.9	1.6–5.2	< 0.001
Extensive colitis	10.0	2.4–41.5	0.001	9.5	2.3–39.4	0.002
C. difficile infection						
Elderly-onset	2.2	1.2–3.8	0.008	-	-	-
Left-sided colitis	6.9	1.6–29.6	0.009	6.9	1.6–29.8	0.009
Extensive colitis	9.6	2.3–39.9	0.002	9.2	2.2–38.4	0.002
COPD	4.9	1.6–15.4	0.007	4.9	1.5–15.7	0.008
Liver cirrhosis	6.8	1.7–26.8	0.006	6.0	1.5–24.7	0.012
Hospitalisation for UC exacerbation						
Elderly-onset	1.4	1.0–2.0	0.038	-	-	-
Left-sided colitis	4.1	2.7–6.4	< 0.001	4.0	2.6–6.1	< 0.001
Extensive colitis	7.5	5.0–11.3	< 0.001	6.4	4.2–9.7	< 0.001
CMV infection	9.5	4.2–21.2	< 0.001	7.4	3.2–17.0	< 0.001
C. difficile infection	25.7	6.2–107.1	< 0.001	18.5	4.4–77.7	< 0.001
Heart disease	1.6	1.0–2.5	0.045	-	-	-
Renal insufficiency	2.1	1.0–4.2	0.041	-	-	-
UC-related mortality						
Elderly-onset	10.4	1.7–63.0	0.010	-	-	-
Current smoker	15.5	1.6–150.4	0.018	-	-	-
Cerebrovascular disease	18.7	3.0–114.8	0.002	7.1	1.0–49.3	0.046
Heart disease	22.2	3.7–135.1	0.001	11.4	1.7–75.4	0.012

OR, odds ratio; CI, confidence interval; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; UC, ulcerative colitis.

Table 4. Dysplasia and colorectal cancer.

	Elderly-onset	Non-elderly-onset	*p*-Value
CRC [*n*, %]	5 [3.2]	10 [0.9]	0.033
SIR of CRC [95% CI]	0.4 [0.0–2.4]	0.9 [0.2–2.6]	
Adenoma [*n*, %]	44 [28.6]	127 [12.0]	< 0.001
Adenoma-related HGD/CRC [*n*, %]	5 [3.2]	8 [0.8]	0.017
Flat dysplasia [*n*, %]	9 [5.8]	86 [8.2]	0.319
Duration of UC at the time of flat dysplasia (median [IQR]) [years]	1 [0–13]	8 [3–13]	0.102

CRC, colorectal cancer; SIR, standardised incidence ratio; CI, confidence interval; HGD, high-grade dysplasia; UC, ulcerative colitis; IQR, interquartile range.

Table 5. Rate of flat dysplasia.

	Shorter UC duration [< 8 years]	Longer UC duration [≥ 8 years]	*p*-Value
Non-elderly-onset [*n*, %]	10 [2.9%]	76 [11.0%]	$p < 0.001$
Elderly-onset [*n*, %]	4 [5.5%]	5 [6.2%]	p = 1.000

UC, ulcerative colitis.

elderly-onset patients had flat dysplasia with shorter disease duration. Contrary to common belief, elderly-onset UC patients appeared to have worse disease outcomes and poorer prognosis than non-elderly-onset patients, and deserve special attention.

To date, data on population-based studies on elderly-onset IBD are available from only two cohorts in the West, the EPIMAD cohort from France and the Veszprem cohort from Hungary.[17] Our study represents the first territory-wide Asian data on elderly-onset UC, showing that elderly-onset UC patients are increasing. At present, data after 2010 are scarce. In our cohort, more than 20% of new UC cases were diagnosed among the elderly after 2010, which was significantly more than that before 2010 [$p < 0.001$], indicating that elderly-onset UC is a rising problem. Although ageing of the population may be a reason, this cannot explain the increasing age-specific incidence among elderly-onset patients. As environmental factors play more important roles in disease onset among older people,[4] increasing numbers of elderly-onset UC may reflect the change in environmental factors during recent decades. As all of the patients included in our Registry are Hong Kong residents, this is not likely to be due to Chinese citizens from mainland China migrating to Hong Kong for better medical care. Although Hong Kong has had a stable and well-developed healthcare system during the past decades, enhanced awareness of disease may in part contribute to the increase in UC incidence.

The proportion of ex-smokers was significantly higher in patients with disease onset at an older age [Table 1] [Supplementary Table 1, available at *ECCO-JCC* online] and there was a trend towards a reducing rate of positive family history with increasing age of disease onset. Our results were consistent with previous studies[26,27,28] showing that former smoking status was a risk factor in elderly-onset disease, and might reflect the decreasing impact of genetic factors on disease onset in the elderly.

In our cohort, there were no significant differences in disease extent at diagnosis, whereas significantly more elderly-onset patients had progression of disease extent during follow-up. The proportion of progression from proctitis to extensive colitis among elderly-onset patients was more than twice as much as that among non-elderly-onset patients. Disease severity, medical treatments, and rates of surgery for UC were similar between patients with elderly-onset and non-elderly-onset disease. The data were however different from those reported by Western countries, which showed elderly patients followed a less aggressive disease course.[17,26,29,30] The proportions of extensive colitis [54.4%] and requirements for systemic steroids [53.5%] and immunosuppressants [26.6%] among elderly-onset patients were higher in our cohort, compared with previous results [28–33% extensive colitis, 17–40% systemic steroids, 3–15% immunosuppressants]. Our results were highly consistent with a recent Japanese study [69.6% extensive colitis, 48.7% steroids, 30.4% immunosuppressants in elderly-onset patients].[9] A Korean study also reported that disease course and prognosis were not different between elderly-onset and non-elderly-onset patients.[31] Whether these discrepancies resulted from ethnic differences between eastern and western countries remains to be determined.

Our results showed that elderly-onset patients had higher risks of CMV and *C. difficile* infections. CMV and *C. difficile* are common pathogens for opportunistic infections, which cause disease in patients with a weakened immune system.[32] Previous studies have found older age was a risk factor for opportunistic infections.[33,34] However, few studies evaluated the association between disease extent and CMV or *C. difficile* infection.[35,36] Our results showed extensive colitis was an independent risk factor for both CMV and *C. difficile* infections. Steroid use and immunosuppressant use were reported as risk factors for opportunistic infections by previous studies.[33,37,38] We also found a trend in our cohort that patients who had received systemic steroids or immunosuppressants within 3 months were more likely to have CMV or *C. difficile* infection [data not shown]. As the majority of elderly-onset patients had extensive colitis, and many of them were exposed to systemic steroids and immunosuppressants in our cohort, they might be more likely to suffer from CMV and *C. difficile* infections.

Significantly more elderly-onset patients in our cohort were hospitalised for UC exacerbation. Although elderly onset was not an independent risk factor, a large proportion [> 85%] of left-sided or extensive colitis and a greater likelihood of opportunistic infections among elderly-onset patients could cause more hospitalisation in this group. Our results were consistent with previous studies which showed that extensive colitis was an independent risk factor for hospitalisation,[39,40] and that CMV or *C. difficile* infection could result in exacerbation of disease, more hospitalisation, longer hospital stay, and even higher mortality in IBD patients.[34, 41, 42]

The SMR of elderly-onset patients was 0.5 [95% CI 0.3–0.9] and that of non-elderly-onset patients was 0.8 [95% CI 0.5–1.4].

The overlap of 95% CI between the two groups suggested no significant difference between both groups. The higher absolute all-cause mortality rate in elderly-onset patients may be mainly attributed to the older age of patients in this group. Elderly-onset patients had a higher risk of death related to UC than non-elderly-onset patients, which was in keeping with previous studies.[7,16,19,43,44] Postoperative complications and mortality occur predominantly among elderly patients with multiple comorbidities.[16,19,43,44] Among patients who had colectomy in our study, 10% [1 out of 10] of elderly-onset patients [and none of the 52 non-elderly-onset patients] died of complications after surgery. We further explored the underlying causes of UC-related mortality. Results showed comorbid cerebrovascular accidents and heart diseases were independent risk factors, indicating that a higher rate of UC-related mortality in elderly-onset patients might be attributed to more comorbidities.

The proportion of CRC in our cohort was 1%. Risk of CRC in our cohort [SIR 0.7, 95% CI 0.2–1.9]was not significantly different from in the general population. Our results were consistent with previous studies.[45,46] The SIR of CRC in elderly-onset and non-elderly-onset patients were 0.4 [95% CI 0.0–2.4] and 0.9 [95% CI 0.2–2.6], respectively. The overlap of 95% CI between the two groups suggested no significant difference between both groups. As a number of UC patients also develop CRC from adenoma, detection and removal of adenoma under colonoscopy for UC assessment might decrease the risk of developing CRC through this pathway. Previous studies found that adenoma in UC may be related to worse outcomes[47,48]. A recent Dutch study compared 5-year cumulative risk of advanced neoplasia [HGD or CRC] among IBD patients with adenoma, IBD patients without adenoma, and adenoma patients without IBD, and concluded that IBD patients with adenoma had a higher risk of developing advanced neoplasia than other two groups of patients.[49] Therefore, elderly-onset UC patients who have an increased risk for adenoma, may have higher risk of developing advanced neoplasia and need more attention.

Although the rates of flat dysplasia were similar, the role of disease duration might be different between the two groups. Only 2.9% of non-elderly-onset patients had flat dysplasia within 8 years of disease duration, whereas the proportion was 5.5% in elderly-onset patients. Although elderly onset is not considered as a risk factor for flat dysplasia in UC patients,[45,50,51] some previous studies found that IBD diagnosed at an older age was associated with early CRC, and suggested earlier surveillance among these patients.[18,52] However, as older age is a well-known risk factor for dysplasia and CRC,[53] it might be older age, rather than elderly-onset UC, that contributed to dysplasia among these patients.

Our study has some limitations. Firstly, as in most registries, data were likely to be sparse in the beginning and to continue to improve over time. Missing data were inevitable. Some of data in this study were retrospectively collected from patients' medical records, such as UC extent and smoking status at diagnosis of patients diagnosed before 2013. We also obtain data from patient interviews. Due to missing data, 125 cases [10%] were excluded in analysis on smoking status and 19 cases [2%] were excluded in analysis on disease extent at diagnosis. Bias could exist, but is unlikely to change the overall results. Moreover, data of early years were likely to be influenced by incompleteness or lack of appropriate diagnostic work at the clinical practice level. Second, as only patients with UC duration ≥ 2 years and were regularly followed up at the 13 major public hospitals after 2011 were included, it is possible that some patients with mild disease course or those who did not seek medical management in these hospitals may be excluded from analysis. Third, drug compliance was not able to be evaluated in this study. Although most physicians excluded intestinal infections before prescribing systemic steroids, some patients self-prescribed steroids when symptoms occurred. These may also lead to bias in analysis. Fourth, most of [> 95%] the patients included in our Registry had disease onset at ≥ 18 years of age. Paediatric-onset patients, among whom the natural course is known to be more severe,[4] only took a very small part in the non-elderly-onset group. Fifth, as the sample size of elderly-onset patients was modest, it was underpowered for some subgroup analyses such as flat dysplasia. Last, there is no defined or structured surveillance programme for UC in Hong Kong and this holds true for most countries in Asia. If and how surveillance was performed for each UC patient was largely dependent on the individual physician's practice and discretion. Therefore our data reflect real-life clinical practice. As older age is a confounding factor for dysplasia, caution should be taken in interpreting that more elderly-onset patients had flat dysplasia with shorter disease duration.

In conclusion, elderly-onset UC patients are increasing over time. With more comorbidities and larger numbers of extensive colitis and steroids and immunosuppressants use, these patients have higher risk of opportunistic infections and hospitalisation than non-elderly-onset patients. SMR and SIR for CRC of elderly-onset UC patients appeared better than in the age- and sex-matched general population. The absolute all-cause mortality rate and absolute incidence rate for CRC among elderly-onset patients were, however, significantly higher than those of non-elderly-onset patients. Special attention is needed to optimise disease management and therapeutic strategies in these patients.

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Conflict of Interest

None.

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Author Contributions

HYS: study concept and design, acquisition of data, analysis and drafting of the manuscript; SCN: study supervisor, study concept and design, analysis and interpretation of the data, critical revision of manuscript; MH: study concept and design, critical revision of manuscript; FKLC, JCYW, and JJYS: critical revision of the article for important intellectual content, final approval of the revision to be submitted.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

References

1. Danese S, Fiocchi C. Ulcerative colitis. *N Engl J Med* 2011;**365**:1713–25.
2. Sartor RB. Microbial influences in inflammatory bowel diseases. *Gastroenterology* 2008;**134**:577–94.

3. Molodecky NA, Soon IS, Rabi DM, *et al.* Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 2012;**142**:46–54.
4. Ruel J, Ruane D, Mehandru S, *et al.* IBD across the age spectrum: is it the same disease? *Nat Rev Gastroenterol Hepatol* 2014;**11**:88–98.
5. Ha CY, Katz S. Clinical implications of ageing for the management of IBD. *Nat Rev Gastroenterol Hepatol* 2014;**11**:128–38.
6. Duricova D, Burisch J, Jess T, *et al.* Age-related differences in presentation and course of inflammatory bowel disease: an update on the population-based literature. *J Crohns Colitis* 2014;**8**:1351–61.
7. Winther K, Jess T, Langholz E, *et al.* Survival and cause-specific mortality in ulcerative colitis: follow-up of a population-based cohort in Copenhagen County. *Gastroenterology* 2003;**125**:1576–82.
8. Lynch RW, Lowe D, Protheroe A, *et al.* Outcomes of rescue therapy in acute severe ulcerative colitis: data from the United Kingdom inflammatory bowel disease audit. *Aliment Pharmacol Ther* 2013;**38**:935–45.
9. Matsumoto S, Miyatani H, Yoshida Y. Ulcerative colitis: comparison between elderly and young adult patients and between elderly patients with late-onset and long-standing disease. *Dig Dis Sci* 2013;**58**:1306–12.
10. Takeuchi K, Smale S, Premchand P, *et al.* Prevalence and mechanism of nonsteroidal anti-inflammatory drug-induced clinical relapse in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2006;**4**:196–202.
11. Katz S, Surawicz C, Pardi DS. Management of the elderly patients with inflammatory bowel disease: practical considerations. *Inflamm Bowel Dis* 2013;**19**:2257–72.
12. Cottone M, Kohn A, Daperno M, *et al.* Advanced age is an independent risk factor for severe infections and mortality in patients given anti-tumor necrosis factor therapy for inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2011;**9**:30–5.
13. Akerkar GA, Peppercorn MA, Hamel MB, *et al.* Corticosteroid-associated complications in elderly Crohn's disease patients. *Am J Gastroenterol* 1997;**92**:461–4.
14. Beaugerie L, Brousse N, Bouvier AM, *et al.* Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet* 2009;**374**:1617–25.
15. Kaplan G, Hubbard J, Panaccione R, *et al.* Risk of comorbidities on postoperative outcomes in patients with inflammatory bowel disease. *Arch Surg* 2011;**146**:959–64.
16. Kaplan GG, McCarthy EP, Ayanian JZ, *et al.* Impact of hospital volume on postoperative morbidity and mortality following a colectomy for ulcerative colitis. *Gastroenterology* 2008;**134**:680–7.
17. Charpentier C, Salleron J, Savoye G, *et al.* Natural history of elderly-onset inflammatory bowel disease: a population-based cohort study. *Gut* 2014;**63**:423–32.
18. Baars JE, Kuipers EJ, van Haastert M, *et al.* Age at diagnosis of inflammatory bowel disease influences early development of colorectal cancer in inflammatory bowel disease patients: a nationwide, long-term survey. *J Gastroenterol* 2012;**47**:1308–22.
19. Nicholls RJ, Clark DN, Kelso L, *et al.* Nationwide linkage analysis in Scotland implicates age as the critical overall determinant of mortality in ulcerative colitis. *Aliment Pharmacol Ther* 2010;**31**:1310–21.
20. Lakatos PL, David G, Pandur T, *et al.* IBD in the elderly population: results from a population-based study in Western Hungary, 1977–2008. *J Crohns Colitis* 2011;**5**:5–13.
21. Lennard-Jones JE. Classification of inflammatory bowel disease. *Scand J Gastroenterol* Suppl 1989;**170**:2–6; discussion 16–9.
22. Satsangi J, Silverberg MS, Vermeire S, *et al.* The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006;**55**:749–53.
23. Truelove S, Witts L. Cortisone in ulcerative colitis. *Br Med J* 1955;**2**:1041–48.
24. Dignass A, Eliakim R, Magro F, *et al.* Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 1: Definitions and diagnosis. *JCrohns Colitis* 2012;**6**:965–90.
25. Riddell R, Goldman H, Ransohoff D, *et al.* Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications. *Hum Pathol* 1983;**14**:931–68.
26. Riegler G, Tartaglione M, Carratú R, *et al.* Age-related clinical severity at diagnosis in 1705 patients with ulcerative colitis: a study by GISC [Italian Colon-Rectum Study Group]. *Dig Dis Sci* 2000;**45**:462–5.
27. Ha CY, Newberry RD, Stone CD, *et al.* Patients with late-adult-onset ulcerative colitis have better outcomes than those with early onset disease. *Clin Gastroenterol Hepatol* 2010;**8**:682–7 e1.
28. Gower-Rousseau C, Vasseur F, Fumery M, *et al.* Epidemiology of inflammatory bowel diseases: new insights from a French population-based registry [EPIMAD]. *Dig Liver Dis* 2013;**45**:89–94.
29. Fujimoto T, Kato J, Nasu J, *et al.* Change of clinical characteristics of ulcerative colitis in Japan: analysis of 844 hospital-based patients from 1981 to 2000. *Eur J Gastroenterol Hepatol* 2007;**19**:229–35.
30. Triantafillidis J, Emmanouilidis A, Pomonis E, *et al.* Ulcerative colitis in the elderly: clinical patterns and outcome in 51 Greek patients. *J Gastroenterol* 2001;**36**:312–6.
31. Lee JH, Cheon JH, Moon CM, *et al.* Do patients with ulcerative colitis diagnosed at a young age have more severe disease activity than patients diagnosed when older? *Digestion* 2010;**81**:237–43.
32. Dave M, Purohit T, Razonable R, *et al.* Opportunistic infections due to inflammatory bowel disease therapy. *Inflamm Bowel Dis* 2014;**20**:196–212.
33. Toruner M, Loftus EV Jr, Harmsen WS, *et al.* Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology* 2008;**134**:929–36.
34. Ananthakrishnan AN, McGinley EL, Binion DG. Excess hospitalisation burden associated with Clostridium difficile in patients with inflammatory bowel disease. *Gut* 2008;**57**:205–10.
35. Yi F, Zhao J, Luckheeram R, *et al.* The prevalence and risk factors of cytomegalovirus infection in inflammatory bowel disease in Wuhan, Central China. *Virol J* 2013, Feb 1. doi: 10.1186/1743-422X-10-43.
36. Kaneko T, Matsuda R, Taguri M, *et al.* Clostridium difficile infection in patients with ulcerative colitis: investigations of risk factors and efficacy of antibiotics for steroid refractory patients. *Clin Res Hepatol Gastroenterol* 2011;**35**:315–20.
37. McCurdy JD, Jones A, Enders FT, *et al.* A model for identifying cytomegalovirus in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2015;**13**:131–7; quiz e7.
38. Gauss A, Rosenstiel S, Schnitzler P, *et al.* Intestinal cytomegalovirus infection in patients hospitalized for exacerbation of inflammatory bowel disease: a 10-year tertiary referral center experience. *Eur J Gastroenterol Hepatol* 2015;**27**:712–20.
39. Vester-Andersen MK, Vind I, Prosberg MV, *et al.* Hospitalisation, surgical and medical recurrence rates in inflammatory bowel disease 2003-2011—a Danish population-based cohort study. *J Crohns Colitis* 2014;**8**:1675–83.
40. Tinsley A, Naymagon S, Mathers B, *et al.* Early readmission in patients hospitalized for ulcerative colitis: incidence and risk factors. *Scand J Gastroenterol* 2015;**50**:1103–9
41. Nakase H, Honzawa Y, Toyonaga T, *et al.* Diagnosis and treatment of ulcerative colitis with cytomegalovirus infection: importance of controlling mucosal inflammation to prevent cytomegalovirus reactivation. *Intest Res* 2014;**12**:5–11.
42. Matsumoto S, Yoshida Y. What are the factors that affect hospitalization and surgery for aggravation of ulcerative colitis? *Eur J Gastroenterol Hepatol* 2014;**26**:282–7.
43. de Silva S, Ma C, Proulx MC, *et al.* Postoperative complications and mortality following colectomy for ulcerative colitis. *Clin Gastroenterol Hepatol* 2011;**9**:972–80.
44. Ikeuchi H, Uchino M, Matsuoka H, *et al.* Prognosis following emergency surgery for ulcerative colitis in elderly patients. *Surg Today* 2014;**44**:39–43.
45. Selinger CP, Andrews JM, Titman A, *et al.* Long-term follow-up reveals low incidence of colorectal cancer, but frequent need for resection, among

Australian patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2014;**12**:644–50.
46. Jess T, Simonsen J, Jorgensen KT, *et al*. Decreasing risk of colorectal cancer in patients with inflammatory bowel disease over 30 years. *Gastroenterology* 2012;**143**:375–81 e1; quiz e13–4.
47. Vieth M, Behrens H, Stolte M. Sporadic adenoma in ulcerative colitis: endoscopic resection is an adequate treatment. *Gut* 2006;**55**:1151–5.
48. Kisiel JB, Loftus EV Jr, Harmsen WS, *et al*. Outcome of sporadic adenomas and adenoma-like dysplasia in patients with ulcerative colitis undergoing polypectomy. *Inflamm Bowel Dis* 2012;**18**:226–35.
49. van Schaik FD, Mooiweer E, van der Have M, *et al*. Adenomas in patients with inflammatory bowel disease are associated with an increased risk of advanced neoplasia. *Inflamm Bowel Dis* 2013;**19**:342–9.
50. Jess T, Loftus EV Jr, Velayos FS, *et al*. Risk factors for colorectal neoplasia in inflammatory bowel disease: a nested case-control study from Copenhagen county, Denmark and Olmsted county, Minnesota. *Am J Gastroenterol* 2007;**102**:829–36.
51. Jess T, Rungoe C, Peyrin-Biroulet L. Risk of colorectal cancer in patients with ulcerative colitis: a meta-analysis of population-based cohort studies. *Clin Gastroenterol Hepatol* 2012;**10**:639–45.
52. Karvellas C, Fedorak R, Hanson J, *et al*. Increased risk of colorectal cancer in ulcerative colitis patients diagnosed after 40 years of age. *Can J Gastroenterol* 2007;**21**:443–6.
53. Ku G, Tan IB, Yau T, *et al*. Management of colon cancer: resource-stratified guidelines from the Asian Oncology Summit 2012. *Lancet Oncol* 2012;**13**:e470–81.