The Clinical Features of Elderly-onset Ulcerative Colitis

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Abstract

Ulcerative colitis (UC) has a bimodal age distribution and increasingly recognized as a disease affecting the elderly. This was a retrospective cohort study in which medication use, disease extent, disease severity at the time of diagnosis, hospitalizations rate were evaluated in 87 patients. The natural course of disease was compared between patients with non-elderly onset UC (<60 years of age at diagnosis) and those of elderly-onset UC (≥60 years of age at diagnosis). Sixty-seven patients developed non-elderly onset UC and 20 patients had elderly-onset UC. Atypical clinical presentations of UC of constipation and fever were more frequent among older patients (15% vs. 1.5%, P=0.01 and 15% vs. 2.9%, P= 0.04, respectively). Furthermore, the non-elderly onset group had more severe disease at the time of diagnosis than the elderly-onset group (P=0.001). Overall medication use did not differ significantly between the two groups. As increasing numbers of elderly patients develop UC, there is a need to understand and optimize therapeutic management in this unique population. (J Intern Med Taiwan 2015; 26: 196-205)

Key Words: Clinical presentations, Elderly, Ulcerative colitis

Introduction

Inflammatory bowel disease (IBD) is characterized by chronic and/or relapsing immune activation and inflammation within the gastrointestinal tract. Crohn's disease (CD) and ulcerative colitis (UC) are the two major forms of IBD. Epidemiological studies of IBD have revealed a bimodal distribution of disease onset, whereby a peak in the incidence of disease is observed in the second and third decades of life, followed by a second rise in the elderly[1,2]. The presence of two peaks suggests a complex interaction between genes and environmental factors. Genes may play a more important role in the young whereas environmental factors may be more important in the elderly[3]. Elderly patients with IBD are defined as patients over 60 years of age[4]. Elderly patients with IBD can be those with disease onset after 60 years of age, or those with disease onset before 60 years who have lived to an older age. In western countries, approximately 10-15% of cases of IBD are diagnosed in patients aged >60 years, and 10-30% of the IBD population is over age 60. One-half of patients are diagnosed between 60 and 70 years of age[5].

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diagnosis of IBD in elderly patient, including infections, ischemic colitis, vasculitis, microscopic colitis, colorectal cancer, and drug-associated colitis [particularly non-steroid anti-inflammatory drugs and antibiotics]. Misdiagnosis at initial presentation is more common in elderly IBD patients (60% compared with 15% in the younger population). Diagnosis may be delayed up to 6 years in the elderly, compared with 2 years in younger IBD patients[6].

As the population ages, the incidence of elderly-onset UC is expected to increase; therefore, an appreciation of disease features is essential for optimizing medical management. Treatment of the elderly UC patients is challenging and is often complicated by concomitant medication use, comorbidities, and impaired mobility. In Taiwan, 1260 UC patients were registered in the National Health Insurance from 1998 to 2008. The incidence of UC increased from 0.61/100,000 in 1998 to 0.74/100,000 in 2008[7]. The ratio of male to female patients with UC was 1.64. For age distribution, 27.4% of patients diagnosed with UC were aged >60 years. Of these elder patients, 16% presented in their sixties, 9% in their seventies and 2.4% in their eighties.

Some studies have identified a decreased need for steroids, immunomodulators, and surgery and fewer hospital admissions for flares in cases of late-onset IBD, suggesting a milder disease course[8,9]. However, some studies have shown that IBD-related hospitalizations were associated with substantial morbidity and higher mortality in older patients than in younger patients [10]. Nevertheless the natural history of UC in elderly patients has not been extensively studied. Therefore, there is a significant need to examine the predictive factors that emerge in the course of UC in elder patients, in order to optimize therapeutic management and intervention.

Material and Methods

Patient Population

This retrospective study was conducted at Mackay Memorial Hospital in Taipei, Taiwan, between January 2000 and December 2014. All UC patients treated continuously over a period of at least one year (n=87) were included. A diagnosis of UC was based on classical clinical symptoms and was supported by endoscopic and histologic findings, as well as stool examinations to identify infectious causes. Special attention was paid to the clinical and laboratory details of the elderly people to exclude the possibility of indeterminate colitis, diverticulosis, ischemic colitis, and primary neoplasms. The date of initial UC diagnosis was confirmed by review of initial diagnostic endoscopic data, pathology reports, and radiographic studies. None of the patients at our hospital had received any prior treatment or were previously diagnosed. The study protocol was approved by our hospital's Ethics Committee for Human Studies. Informed consent and assent were obtained from parents before entry of patient's information.

Data Collection

Age at initial diagnosis was used to categorize patients into non-elderly onset and elderly-onset UC groups. Patients diagnosed between the ages of 15 and 59 were assigned to the non-elderly onset, and those diagnosed at or after age 60 were assigned to elderly-onset UC group. Demographic information that we reviewed included gender, smoking history (with patients categorized as smokers or non-smokers) and age at UC diagnosis. UC-related medication use, disease extent, disease severity at the time of diagnosis, extraintestinal manifestations (EIMs), hospitalization for colitis flares, colectomies, and mortality rate were documented. Medications that were reviewed included 5-aminosalicylic acids ([5-ASA] oral, enema, or suppository), steroids (oral, enema, or intravenous), immunomodulators (azathioprine, methotrexate, and cyclosporine), and adalimumab. Patients were classified as having been exposed to a medication if treatment was started any time after diagnosis or during the follow-up

period. EIMs were defined as enteropathic arthritis, erythema nodosum, pyoderma gangrenosum, and/or primary sclerosing cholangitis.

Outcome Measures/Variables Descriptions

UC localization at diagnosis and maximum follow-up was classified according to the Montreal classification [11]. Ulcerative proctitis (E1) was defined as involvement limited to the rectum (i.e., proximal extent of inflammation distal to the rectosigmoid junction). Left-sided UC (E2) was defined as involvement limited to the portion of the colorectum distal to the splenic flexure. Extensive UC (E3) was defined as involvement extending proximally to the splenic flexure. Disease symptom severity at the time of diagnosis was categorized using the modified Truelove and Witts Severity Index, as follows: mild ulcerative colitis was defined as fewer than 4 bowel movements daily; moderate ulcerative colitis was defined as more than 4 daily bowel movements without the patient being systemically ill; and severe ulcerative colitis was defined as more than 6 bowel movements daily with patient also being systemically ill (tachycardia, fever, anemia, or a raised erythrocyte sedimentation rate)[12].

Statistical Analysis

Each patient's initial visit was logged as the enrollment visit and all subsequent visits were logged as follow-up visits. Patients with no follow-up visits or one follow-up visit that occurred less than 1 year after enrollment were excluded. Descriptive statistics for continuous variables were calculated and are reported as means and standard deviations (SD). The categorical variables are described using frequency distributions and are reported as n (%). P values are based on a t-test for continuous variables and chi-squared or Fisher's exact test was for categorical variables. Statistical analysis was performed using the Statistical Package for the Social Science SPSS for Windows, version 12.0 (SPSS Inc., Chicago, IL). Tests were two-tailed, with a significance level of 0.05. The 'event' of first UC-related major abdominal surgery was evaluated using survival analysis. The time to first surgery was considered to begin at the date of UC diagnosis and end at the date of occurrence of the 'event' or last known follow-up. The cumulative probabilities of event-free survival were estimated using the proportional hazard regression mode.

Results

Ninety-four UC patients with a median follow-up time of 5.1 ± 2.3 years were identified during the 15-year study period. Seven patients diagnosed with UC were lost to follow-up. Among the remaining UC patients, 87 had a follow-up time equal to or greater than 1 year. Sixty-seven patients (77%) were identified having non-elderly onset UC and 20 patients (23%) had elderly-onset UC. The average age at diagnosis was 44 years. The age distribution at diagnosis did not show a bimodal distribution and the peak age was in the fourth decade. (Figure 1)

The most common symptoms were rectal bleeding (37.8%), abdominal pain (28.7%), and diarrhea (24.1%)(Table 1). With regard to disease location at diagnosis, pancolitis (E3) was the most common (36.8%), followed by proctitis (E1) (35.6%) and left-sided colitis (E2) (27.6%). Clinical characteristics are listed in Table 1. The median follow-up time was 5.6±2.4 years (interquartile range (IQR) 1-22) in patients with non-elderly onset UC and 3.5±1.6 years (IQR 1-14) in those with elderly-onset UC; this difference was no significant (P=0.29).

The ratio of male to female ratio patients was 1.39 in non-elderly onset UC and 1.5 in those with elderly-onset UC. No patient had a family history of UC or colon cancer during follow up. Patients with non-elderly onset were more likely to be non-smokers, while more patients with elderly-onset UC were smokers. However, the difference was not statistically significant (P=0.15).

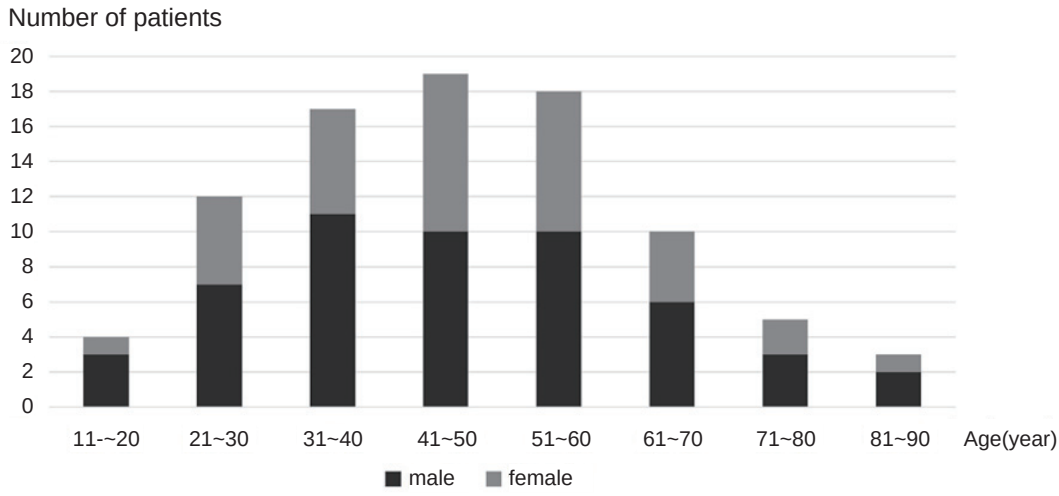

Figure 1. Age distribution at diagnosis of UC study population.

Table 1. Demographics and characteristics of all patients

	N	%
Sex		
male	51	58.6
Female	36	41.4
Smoking habit		
Nonsmokers	74	85.1
Smokers	13	14.9
Disease extent		
Ulcerative proctitis (E1)	32	36.8
Left-sided UC (E2)	24	27.6
Extensive UC (E3)	31	35.6
Severity of initial UC diagnosis		
Mild (S1)	9	10.4
Moderate (S2)	33	37.9
Severe (S3)	45	51.7
Initial symptoms		
Rectal bleeding	59	37.8
Abdominal pain	25	28.7
Diarrhea	21	24.1
Fistula formation	4	4.6
Constipation	4	4.6
Fever	5	5.7
Colon cancer	0	0
Family history	0	0

Disease Location, Behavior and Outcome

There were no significant differences observed for symptoms representing clinical severity, such as bleeding, pain, diarrhea and fistula formation (68.7% vs. 65%, P=0.66; 28.4% vs. 30%, P= 0.99; 23.9% vs. 25%, P= 0.91; and 5.9% vs. 0%, P=0.26 respectively). (Table 2) Conversely, atypical clinical presentations of constipation and fever were frequent among older patients (15% vs. 1.5%, P=0.01 and 15% vs. 2.9%, P=0.04 respectively). With regard to disease severity at initial diagnosis, the non-elderly onset group had greater disease activity than the elderly-onset group (S3 62.7% vs. 15%, P=0.001). With regard to disease localization, most older patients had proctitis (E1) (10/20, 50%). In contrast, non-elderly patients had more extensive UC (E3) (27 /60, 40.3%), although the difference was no statistically significant (P=0.21). At study entry, 91% of the patients received treatment with oral 5-aminosalicylic acid (5-ASA), 54% received oral steroids, 8% received immunomodulators (e.g., cyclosporine/azathioprine), and 3% received adalimumab. In terms of overall medication use during the course of disease, there were no statistically significant differences between the two groups, although rates of intravenous steroids, immunomodulator and

Table 2. Comparisons of characteristics between non-elderly onset and elderly-onset UC patients

	Non-elderly onset		Elderly-onset		p-value
	N	(%)	N	(%)	
Number of patients	67	77	20	23	
Gender (M)	39	58.2	12	60	0.88
Mean age (yrs ± SD)	39.4 ± 12.1		69.7 ± 7.7		
Range (yrs)	15-59		60-83		
Follow-up (yrs ± SD)	5.6 ± 2.4		3.5 ± 1.6		0.29
Range (yrs)	1-22		1-14		
Smoking history	8	11.9	5	25	0.15
Disease extent					
Proctitis (E1)	22	32.8	10	50	0.21
Left-sided UC (E2)	18	26.9	6	30	
Extensive UC (E3)	27	40.3	4	20	
Symptom					
Rectal bleeding	46	68.7	13	65	0.66
Abdominal pain	19	28.4	6	30	0.99
Diarrhea	16	23.9	5	25	0.91
Fistula formation	4	5.9	0	0	0.26
Constipation	1	1.5	3	15	0.01*
Fever	2	2.9	3	15	0.04*
Symptom severity					
Mild (S1)	5	7.4	4	20	0.001*
Moderate (S2)	20	29.9	13	65	
Severe (S3)	42	62.7	3	15	
Admission times (mean)	1.8		1.65		0.53
Range	0-14		0-5		
Surgery	24	35.8	3	15	0.14
Extra-intestinal manifestations	5	7.4	0	0	0.16

*P values less than 0.05.

adalimumab were slightly higher in patients with non-elderly onset UC (5.9% vs. 0%, P=0.26; 10.4% vs. 0%, P=0.13; 4.5% vs. 0%, P=0.33 respectively). (Table 3) The majority of non-elderly onset (36/67, 53.7%) and elderly-onset (11/20, 55%) patients required an initial course of oral steroid therapy.

Extraintestinal Manifestations

Five patients with non-elderly onset UC (5.7%) had EIMs. Two were diagnosed with enteropathic arthritis, one had sclerosing cholangitis, and two had pyoderma gangrenosum. There were no EIMs in the elderly-onset group. EIMs were not associated with age or gender.

Surgery and Hospitalization

The mean of UC-related hospitalizations was similar among non-elderly onset (1.81) and elderly-onset patients (1.65) during the course of disease (P=0.53). Twenty-four patients in the non-elderly

Table 3. Comparisons of medications during follow-up between non-elderly onset and elderly-onset UC patients

	Non-elderly onset		Elderly-onset		p-value
	N	(%)	N	(%)	
5-ASA compounds					
Oral	61	91.0	18	90	0.88
Rectal	18	26.9	4	20	0.53
Steroid					
Oral	36	53.7	11	55	0.92
Rectal	6	8.9	4	20	0.17
IV	4	5.9	0	0	0.26
Immunomodulators	7	10.4	0	0	0.13
Adalimumab	3	4.5	0	0	0.33

* P values less than 0.05.

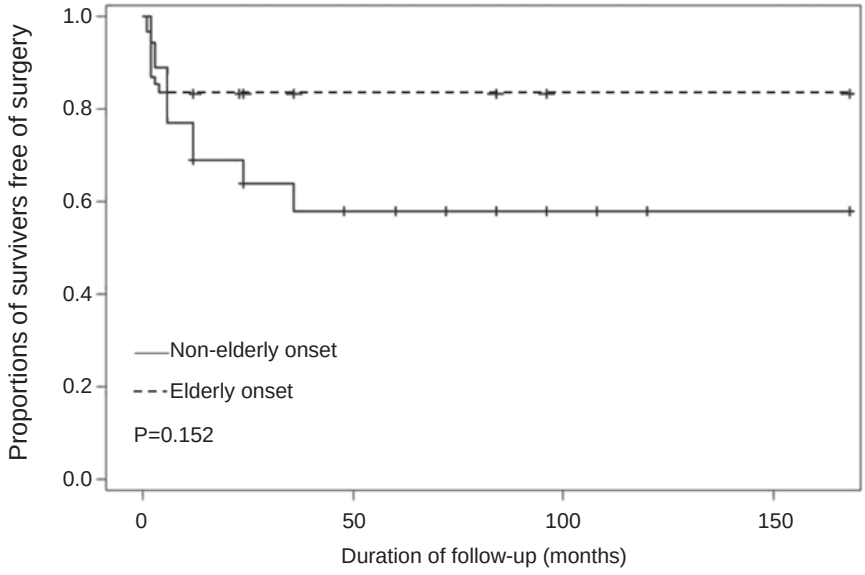

Figure 2. Cox regression analysis of the proportion of survivers free of surgery during follow-up related to diagnosis of UC. There was no difference between non-elderly onset and elderly-onset patients (P=0.152).

onset group underwent surgery at least once during the study period (nine patients had partial colectomy, nine had total colectomy and four patient had fistulectomy), resulting in a crude colectomy rate of 26%. Three elderly-onset patients underwent surgery during the study period (one patients underwent partial colectomy and two patient underwent Hartmann's procedure). The overall survival free of surgery was not significantly different in the non-elderly group compared with elderly group (P=0.152, log-rank; figure 2).

Discussion

This study employed a retrospective cohort analysis to compare non-elderly onset with elderly-onset UC patients in terms of disease risk factors, extent of disease, disease severity, treatment and outcomes. The age distribution at diagnosis did not

follow a bimodal distribution in our study. Similar findings were reported in a population-based study in Taiwan, which found that the male incidence rate peaked at age 50-59, and the female incidence rate peaked at age 70-79, without bimodal distribution[13]. IBD is believed to result from interaction between genetic and environmental factors. Environmental may play a more important role in the elderly[3]. A number of environmental risk factors have been explored, including smoking, appendectomy, oral contraceptives use, diet, breastfeeding, infections, vaccinations, antibiotics, and childhood hygiene[14].

Tobacco use, and cigarette smoking in particular, is perhaps the most significant environmental risk factor associated with IBD. With regard to the relationship between UC and smoking, one study showed smoking prevalence was significantly lower in UC patients than in the general population (9% versus 28%). That study classified patients diagnosed at age 40 or later as having late-onset UC. Smoking is protective against UC development at any age, particularly early-onset disease. However, a prior history of smoking is associated with a high likelihood of developing elderly-onset UC[15]. In an Italian study of UC patients, the proportions of males and ex-smokers were higher among older-onset patients than among those presenting with UC earlier in life[9]. Our study found fewer smokers in the non-elderly onset UC cohort, but the difference was not statistically significant (P=0.15).

Our findings are consistent with results previously published results demonstrating that elderly-onset UC was associated with less extensive disease [9,16,17]. A study of 1705 UC patients study showed that rates of proctitis and distal colitis tended to increase among patients diagnosed at age 50 years or older (P =0.02 and P =0.019, respectively)[9]. Zimmerman et al. reported a greater occurrence of distal localization in elder patient[16]. The clinical features of elderly-onset UC are non-specific; therefore, establishing the correct diagnosis is a challenge. However, failure to consider a diagnosis of UC can lead to delays in initiating the appropriate treatment and result in potentially preventable complications and persistent morbidity. Colonoscopy should be performed in the elderly in order to rule out other possible disorders that are compatible with abdominal symptoms. Our study revealed that atypical clinical presentations of constipation and fever were frequent among older patients. One report described initial symptoms characterized mainly by diarrhea rather than rectal bleeding in the elderly[16]. Other studies have shown that symptoms of rectal bleeding and diarrhea may be less common in elderly patients, but UC may also have atypical forms of presentation, such as constipation[9,18].

A notable finding of our study was that the elderly-onset group had less severe disease at initial diagnosis of UC than the non-elderly onset group (P=0.001). This result is compatible with a study that found disease severity at initial presentation was higher in younger patients, when assessed by diarrhea frequency, the presence of pancolitis, and the use of steroids[17]. Aloi M. et al. reported extensive and severe disease upon diagnosis in cases of pediatric UC, with a high overall rate of disease extension at follow-up[19]. Additionally, since elderly UC patients are more likely to have mild disease severity and atypical presentations of fever and constipation, the diagnosis in geriatric populations may be delayed.

Therapeutic approaches for UC in this unique population have been based on expert opinion and data extrapolated from clinical trials that may or may not have included elderly patients. The elderly population, independent of functional status, is often excluded due to co-morbidities and polypharmacy, and concern about drug interactions. When choosing treatments, maintaining adequate nutritional status is important. Malnutrition is relatively common in older populations, and can also affect treatment tolerance and increase the risk of

infections. One review study shows that there is insufficient evidence to evaluate either the efficacy of treatment for UC in the elderly or the risk of treatment-related adverse events[20]. Mesalamine given at a dose of 2.4 g/d is usually effective for elderly patients, and a once daily dosing is reasonable[21]. Using topical agents is difficult due to physical limitations and anal sphincter incompetence.

Glucocorticosteroids have been the mainstay of treatment for acute flare-ups of UC. The elderly are especially prone to hypertension, hypokalemia, hyperglycemia, and mental status changes. Furthermore, osteoporotic-related fractures are especially common in the elderly IBD population, with a prevalence approaching 15%[22]. A cohort study of 295 patients found that elder UC patients were more likely to experience steroid-free remission at 1 year than younger patients (64% vs. 49%; $P=0.01$)[23]. In patients who do not respond to oral glucocorticoids, the addition of immunomodulatory drugs (azathioprine and 6-mercaptopurine) or anti-tumor necrosis factor (TNF) antibodies can be considered. We are not aware of any randomized controlled trials of anti-TNFα or immunosuppressant therapy that reported subgroup analysis results by age[20]. One study of 500 patients has shown that 3 out of 5 deaths attributable to infliximab treatment were in patients older than 60 years[24]. In our study, elderly-onset UC patient did not use immunosuppressive or anti-TNFα treatment due to concern about risks of infection and malignancy.

When medical therapy does not succeed, or a patient develops toxic megacolon, obstruction, fistula formation or incessant bleeding, surgery may be necessary. Recent reports suggest that clinical indications for surgery in elderly patients with UC should not differ from those for younger patients. However, urgent surgery in the elderly was also a predictor of poor survival[25]. Elderly patients were hospitalized more often during a first attack of UC and were more likely to receive systemic steroids. No elderly patients required urgent surgery, and no patient in either group died of UC or related complications. The prognosis for UC in the elderly is the same as in younger patients [26].

It has been reported that male gender, severity, and longstanding disease are risk factors of UC-associated colorectal cancer (CRC). The estimated cumulative risk of UC-associated CRCs was 0.7% for patients who had UC for 10 years, 7.9% for patients who had UC for 20 years, and 33.2% for patients who had UC for 30 years [27]. The mean age at the time of diagnosis with CRC was 49.6 years, and the mean duration of UC prior to the development of CRC was 11.5 years[27]. Therefore, older patients with longer disease duration should be placed under colonoscopic surveillance. In Taiwan, a population-based study found that 0.24% of UC patients developed incident CRC, and most of them were male[13]. No patients in our study had CRC, but our sample size was small.

Our study has several strengths, including our use of the Montreal classification to characterize the extent of disease. We also included patients in all age ranges in our analyses. There are important limitations of our study as well. First, we examined a small number of patients. Second, our study employed a retrospective, single-center design. We cannot exclude selection bias during patient enrollment, since some patients were referred to us because of severe comorbidities. Finally, variability in practice among the treating physicians may also have affected patient outcomes.

Conclusion

Elderly UC patients are more likely to have atypical clinical presentations such as fever and constipation and to exhibit less severe illness upon initial diagnosis, which may result in a delayed diagnosis. The course of disease and the basic principles of clinical management in geriatric populations do not differ from those in younger patients.

However, elderly patients should be carefully monitored when medical therapy begins, due to concern about comorbidities and side effects.

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老年人潰瘍性腸炎的臨床特徵

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摘 要

潰瘍性腸炎具有雙峰年齡分佈特色，臨床上有越來越多老年人才發作的潰瘍性腸炎。這是一篇回顧性的研究，分析87例患者用藥，病變範圍，嚴重程度，與住院率。比較潰瘍性腸炎在非老年期發病(診斷年齡<60歲)和老年發病(診斷年齡≥60歲)的差異。其中有67例非老年發病和20例患者老年發病的潰瘍性腸炎。老年患者常有不典型的的臨床表現如便秘，發燒(15% vs. 1.5% P =0.01; 15% vs. 2.9% P = 0.04)。非老年比老年人在發病初期症狀較為嚴重(P = 0.001)。在整體藥物使用方面，2組間無統計差異。隨著老年族群的增加，臨床醫師有必要在這個獨特的族群做適當的治療與了解。