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REVIEW

Epidemiology, demographic characteristics and prognostic predictors of ulcerative colitis

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Abstract

Ulcerative colitis (UC) is a chronic disease characterized by diffuse inflammation of the mucosa of the colon and rectum. The hallmark clinical symptom of UC is bloody diarrhea. The clinical course is marked by exacerbations and remissions, which may occur spontaneously or in response to treatment changes or intercurrent illnesses. UC is most commonly diagnosed in late adolescence or early adulthood, but it can occur at any age. The incidence of UC has increased worldwide over recent decades, especially in developing nations. In contrast, during this period, therapeutic advances have improved the life expectancy of patients, and there has been a decrease in the mortality rate over time. It is important to emphasize that there is considerable variability in the phenotypic presentation of UC. Within this context, certain clinical and demographic characteristics are useful in identifying patients who tend to have more severe evolution of the disease and a poor prognosis. In this group of patients, better clinical surveillance and more intensive therapy may change the natural course of the disease. The aim of this article was to review the epidemiology and demographic characteristics of UC and the factors that may be associated with its clinical prognosis.

Key words: Ulcerative colitis; Incidence; Prevalence; Risk factors; Predictive factors

Core tip: Ulcerative colitis has gained importance over the past few decades due to its increasing incidence rate worldwide. This condition is a chronic disease that affects quality of life, and it can lead to death if not treated properly. Over the past few decades, advances in treatment have provided benefits for patients, including a reduction in mortality. Due to phenotypic variability, different therapeutic modalities may be used. It is important to recognize the factors associated with a more severe clinical course so that clinical decisions can be made as early as possible.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic disease that is characterized by diffuse inflammation of the rectal and colonic mucosa. UC involves the rectum in 95% of cases and may be extended continuously and circumferentially to more proximal parts of the large intestine. The clas-

sic clinical symptom of UC is the presence of bloody diarrhea. The clinical course is characterized by periods of remission and exacerbation, which may occur either spontaneously or in response to treatment[1].

The incidence of inflammatory bowel disease (IBD) has increased in several regions of the world in recent decades, especially in developing nations. Evidence indicates that there is an interaction between genetic and environmental factors in the etiology of the disease[2]. Several studies have shown that certain clinical and demographic characteristics may be associated with different phenotypes and a poor prognosis in UC.

The identification of patients who tend to have more severe evolution of UC is important so that intensive treatments may be started earlier, with the goal of reducing complications and mortality.

The aim of this article was to review the epidemiology and demographic characteristics of UC and the factors that have been associated with poor prognostic outcomes.

EPIDEMIOLOGY AND DEMOGRAPHIC CHARACTERISTICS

Incidence and prevalence

The occurrence of UC worldwide has increased over the past few years. In contrast to the developed countries of North America and Western Europe, where the incidence of UC has plateaued or even decreased[3,4], publications show that the number of cases has increased in developing countries, such as those in Latin America, Asia and Eastern Europe[5-7]. Despite the increased incidence in these places, there are still differences in UC incidence and prevalence in different regions of the world. The incidence rate of UC may vary from 0.5 to 31.5 per 100000 people each year, depending on the studied population[8].

The prevalence is lower in developing countries. In Asian populations, for example, the prevalence ranges from 5.3 to 63.6 per 100000 people[9,10], whereas in North America, it ranges from 37.5 to 238 per 100000 people[11]. In addition to the gradient between the occurrence of UC in the West and in Asian countries, it has been noted that in Europe, although there are exceptions, there is also a geographical gradient for the incidence of IBD, with higher rates in the north and a lower frequency in the south[12]. Similarly, Sonnenberg *et al*[13] suggested a greater frequency of IBD in the northern United States compared with the south of the country. In Latin America, the prevalence of UC also appears to be variable. A study conducted in Puerto Rico suggested that the prevalence of UC is 12.53 cases per 100000 people[5]. Victoria *et al*[14] concluded that the prevalence of UC in a southeastern region of Brazil has been increasing in recent years and that during the period from 2001 to 2005, the prevalence was 14.81 cases per 100000 habitants.

Mortality

According to previous studies, the mortality rate of patients with UC was higher in the first half of the twentieth century. Beginning in the mid-1950s, despite the ongoing increase in incidence, it appears that there has been a drop in the number of deaths, possibly due to the usage of corticosteroids and sulfasalazine and the optimization of surgical techniques[15]. Despite this progress, data published in the 1980s showed that mortality in UC was higher than in the general population[16]. Fortunately, overall, individuals with UC currently have mortality rates similar to or only slightly higher than the rate in the general population[17,18]. This outcome may have been a consequence, among other factors, of the increased use of immunosuppressive therapy in recent years. However, when considering only the UC population, it is clear that mortality is higher in certain subgroups, and especially in newly diagnosed patients and in patients with extensive colitis[17].

In meta-analyses of population-based cohort studies reported by Jess *et al*[20], five of 10 studies reported on UC-related mortality. The authors reported that among patients with UC, the mean percentage of deaths ascribed to UC itself was 17% (range 11% to 30%). In this subgroup of patients, the most common causes of death were colorectal cancer (CRC) (mean 37%, range 24% to 44%) and surgical or postoperative complications (mean 44%, range 17% to 100%). The remaining causes were primarily related to severe disease, *i.e.*, toxic megacolon, intestinal perforation, intestinal infarction, myocardial infarction secondary to anemia and end-stage liver disease due to primary sclerosing cholangitis. Additionally, the authors concluded that compared with general population, patients with UC are at an increased risk of dying of gastrointestinal diseases (OR = 2.5; 95%CI: 1.9-3.2; $P < 0.001$), nonalcoholic liver diseases (OR = 4.0; 95%CI: 2.5-6.5; $P < 0.001$), pulmonary embolisms (OR = 4.0; 95%CI: 1.5-8.7) and respiratory diseases (OR = 1.6; 95%CI: 1.3-2.0; $P < 0.001$), counterweighted by decreased mortality from pulmonary cancer (OR = 0.3; 95%CI: 0.1-0.9; $P = 0.04$). The overall mortality rate due to malignancy was not increased in UC, although there was a trend toward more frequent CRC (standardized mortality ratio = 1.9; 95%CI: 1.0-3.8; $P = 0.07$). The mortality rate due to hematological malignancy, and specifically leukemia and non-Hodgkin's lymphoma, were not increased[17].

In an Australian study performed in 401 patients with UC, Selinger *et al*[19] concluded that the major causes of death were circulatory ($n = 42$; 44.2%), malignant ($n = 22$; 23.2%), digestive ($n = 11$; 11.6%) and respiratory ($n = 7$; 7.4%) diseases. Mortality from circulatory diseases was significantly more common in UC than in the general population [44.2% *vs* 33.8%; $P = 0.0001$; RR = 1.38 (95%CI: 1.11-1.72)], mainly due to ischemic heart disease [24.2% *vs* 15.9%; $P = 0.04$; RR = 2.04 (1.45-2.85)]. Death from cholangiocarcinoma occurred nearly 15 times more often among patients with UC than in the general population [4.3% *vs* 0.3%; $P < 0.0001$; RR = 14.28 (95%CI: 5.40-37.80)]. Fatal CRC was more frequent in UC than in

the general population [6.3% *vs* 2.7%; $P = 0.047$; RR = 2.36 (95%CI: 1.09-5.14)][19].

A Danish cohort study of 36080 patients with UC was performed by Jess *et al*[20]. The authors reported that the overall risk of dying, compared with the risk in the general population, was high in the first year after UC diagnosis (HR = 2.43; 95%CI: 2.31-2.57) and then rapidly declined to a constant level of approximately 1.1 after 2 years. The risk of dying from infectious diseases, cardiovascular diseases, gastrointestinal disorders with or without the inclusion of IBD or CRC remained significantly increased in the long term, with HR estimates of 1.64 (95%CI: 1.24-2.17) for infectious diseases, 1.11 (95%CI: 1.01-1.21) for cardiovascular diseases, 1.26 (95%CI: 1.07-1.48) for gastrointestinal disorders other than UC and 1.47 (95%CI: 1.23-1.76) for CRC[20].

Age

In recent decades, although there has been an increased incidence of UC in different age groups, the majority of patients with UC are in the age group of 30-40 years at diagnosis[11]. It has been observed that the average age at diagnosis is usually slightly higher in Asian countries compared with Western countries[21].

Certain publications indicate that a second incidence peak occurs in an older age group[22,23]. A study by Souza *et al*[24] in southeastern Brazil showed that there was a trend toward a second peak of new hospital admissions due to UC in the age group of 60-69 years old. However, there is no consensus in the literature regarding the existence of this second peak[11].

Although UC is less common in children, recent studies have shown that the number of UC cases has increased in pediatric patients and adolescents. In Scotland, for example, in recent years, an increased incidence of UC in the age group under 16 years was observed. Comparing the periods 1990-1995 and 2003-2008, incidence rates increased from 1.59/100000 per year (95%CI: 1.28-1.94) to 2.06/100000 per year (95%CI: 1.70-2.47; $P = 0.023$)[25]. In a recent publication, Pant *et al*[26] demonstrated that in the United States, between 2000 and 2009, the number of hospitalizations of pediatric patients with UC increased from 4171 to 7127 per year. Lindberg *et al*[27] suggested that the increased frequency of disease is more significant during puberty and adolescence than during childhood. The authors demonstrated that in recent years, although the incidence has increased in the age group of 11-15 years, this rate has remained stable in children under 10 years of age.

Gender

Most UC studies have shown a male predominance or an equal distribution between genders[11,21]. In the past, Italian investigators have even suggested that polymorphisms in an enzyme involved in the signal transduction of insulin (cytosolic low-molecular-weight protein tyrosine phosphatase) could increase predisposition to the development of Crohn's disease (CD) in women and of UC in men[28]. However, this hypothesis was refuted in a more recent study by a group of Spanish investigators[29]. Moreover, in contrast to the cited studies, other authors have found a high female incidence of the disease[30]. In a recent publication describing 35404 cases of IBD, Beteridge *et al*[31] reported a female predominance among patients with UC (RR = 1.35; 95%CI: 1.32-1.39).

PREDICTORS OF PROGNOSIS

Family history

Although a family history of UC is a risk factor for developing the disease, it does not seem to be a negative prognostic factor in patients with UC[32,33].

In a prospective study, Henriksen *et al*[34] found a 10.1% incidence of a family history of IBD among 454 individuals with UC. The authors concluded that although the group with a positive family history had further exacerbations of the disease in five years, there was no significant difference in drug therapy or indication for colectomy. In a retrospective study in 411 children with a diagnosis of IBD, 244 (59.4%) of whom had UC, Roma *et al*[35] concluded that children with familial IBD had an earlier onset of disease compared with those with sporadic IBD. However, this difference had no significant impact on the clinical phenotypes, course and/or outcome of disease. Kuwahara *et al*[36] obtained clinical data for 46114 UC cases. The present age and the age at disease onset were lower among patients with UC who had a family history than among those without a family history. However, the clinical course of patients with UC was not affected by family history.

Environmental factors

Patients with IBD have a genetic predisposition to the development of such diseases. It appears, however, that this predisposition alone is not sufficient for the onset of inflammation. The current belief is that genetically predisposed patients, when in contact with environmental factors, develop an inadequate immune response that ultimately causes inflammation of the gastrointestinal tract[37]. Over time, many studies have attempted to support the hygiene hypothesis, although the data are conflicting, and well-designed prospective studies are needed[38]. Until then, among the studied factors, only smoking and appendectomy have a well-defined influence on the risk of developing UC.

In contrast to what happens in CD, smoking is a protective factor against the development of UC. In a meta-analysis, Calkins concluded that the risk of non-smokers developing UC is approximately three times higher than that of smokers (OR = 2.9; 95%CI: 2.6-3.2)[39]. Moreover, among patients with UC, those who do not smoke have a less favorable evolution of the disease over time[40]. Aldhous *et al*[41] concluded that five years after diagnosis, a decrease in the extent of UC was more common in smokers than in groups of former smokers and non-smokers. Smoking seems to be a protective factor against

colectomy (OR = 0.57; 95%CI: 0.38-0.85) and against the development of CRC (OR = 0.5; 95%CI: 0.2-0.9)[42,43].

Appendectomy influences the emergence of IBD and is considered to be a risk factor for the development of CD[44]. Conversely, in one of the first studies on this topic, Rutgeerts *et al*[45] concluded that appendectomy protects individuals against the emergence of UC. While studying the reason for this protection, Matsushita *et al*[46] suggested that the appendix plays an important role in the pathogenesis of UC. In a meta-analysis, Koutroubakis *et al*[47] concluded that performing an appendectomy reduced the chance of developing UC by 69% (OR = 0.31; 95%CI: 0.261-0.373). Certain studies have also suggested that appendectomy might influence the clinical course of UC by reducing the rate of recurrence of the disease and the need for immunosuppression and colectomy[48-50]. However, the data are still conflicting, and the influence of appendectomy on the clinical course of UC needs to be further investigated in prospective studies.

The intestinal microbiota plays an important role in homeostasis and immune system functioning. Currently, it is believed that different environmental and genetic factors can promote changes in that microbiota. The formation of a pathogenic microflora in genetically predisposed individuals is associated with changes in epithelial function, dysregulation of the immune function of the gastrointestinal tract and persistent intestinal inflammation[51]. Future studies may indicate which environmental factors are associated with the formation of an abnormal microbiota and whether these changes are only the cause or also be consequences of the changes introduced by IBD.

Nutritional factors

Knowledge about nutrition and nutritional status is not only important for the multidisciplinary team that treats patients with IBD but also for the patients themselves, who may have a wide range of questions regarding how nutrition affects their quality of life and the evolution of the disease[52].

Nutritional deficiencies occur in 20% to 85% of patients with IBD, and protein-energy malnutrition is the most common[53,54]. Although malnutrition is often related to CD, studies have shown similar rates of malnutrition between patients with CD and patients with UC[55,56]. Malnutrition in these patients is associated with a poor quality of life and infection and with increased in-hospital mortality, length of stay and financial costs[55,57,58]. It is noteworthy that body mass index (BMI), an indicator commonly used to define nutritional status, has several limitations[59]. Jahnsen *et al*[60] reported that despite finding higher BMI values in patients with UC than in those with CD, lean body mass was not higher than in controls. Furthermore, a higher percentage of fat mass in patients with UC contributed to their increased weight. Therefore, BMI itself has adverse implications for the course of UC[61,62].

Overweight or obese patients with UC have higher rates of colectomy than do eutrophic patients[63], an increased need for permanent ileostomy, longer hospital stays, higher rates of incisional hernia after ileoanal pouch anastomosis[64,65], an increased risk of nonalcoholic fatty liver disease[66] and thromboembolism[67] and increased inflammation of the colon[61]. Increased body weight has also been associated with an early loss of response to infliximab in IBD[68]. In contrast, a study conducted by Markel *et al*[69] did not find any association between preoperative BMI and infectious complication in a postoperative wound in children with UC. In this group, 78% of patients were overweight (BMI > 25) at the time of surgery.

Age at diagnosis

The influence of age at diagnosis on the clinical course of UC is another controversial issue. Therefore, the Montreal classification of UC, in contrast to the classification of CD, does not include age at diagnosis as a criterion. So far, there is no convincing evidence that the creation of subgroups according to age at diagnosis would affect the clinical course of UC patients[70].

Certain authors have evaluated the influence of age at diagnosis on the clinical evolution of patients with UC. Riegler *et al*[71] evaluated 1705 patients with UC in Italy and reported that younger patients had a greater need to use corticosteroids and a higher incidence of diarrhea and weight loss at diagnosis. An important study on the clinical course of UC (IBSEN study), conducted by Norwegian investigators, prospectively evaluated patients with UC for 10 years. Based on multivariate analysis, the authors found that the risk of colectomy in patients with an age at diagnosis of 50 years was 72% lower than in patients under 30 years old (HR = 0.28; 95%CI: 0.12-0.65)[72]. The hypothesis of a milder and less aggressive clinical course in patients with an older age at diagnosis was corroborated by other recent studies[73,74]. In contrast, other studies found no significant differences in prognosis when comparing groups with different ages at diagnosis[75,76].

Extent of disease

According to the Montreal classification, based on location, UC can be classified into three different subtypes: proctitis (when inflammation is restricted to the mucosa of the rectum), left colitis (when inflammation extends beyond the rectum and to the splenic flexure) and extensive colitis (when inflammation reaches the mucosa proximal to the splenic flexure)[70]. The most frequent location of UC may vary between different studies. Left colitis was most frequent in studies conducted in France (extensive colitis: 19.1%; left colitis: 52.3%; proctitis: 28.7%) and Portugal (extensive colitis: 28%; left colitis: 52%; proctitis: 21%)[3,77]. In Asia, it appears that more patients have inflammatory processes limited to the mucosa of the rectum, as demonstrated by Ng *et al*[78] (extensive colitis: 31%; distal colitis: 32%; proctitis: 37%). In a study from southeastern Brazil that evaluated patients

diagnosed with UC in the period from 1980-1999 and in which the applied classification was different from the Montreal classification, the results were similar to those found in the Asian population. The occurrence of extensive colitis was detected in 28.3% of cases, whereas the frequencies of left and proctosigmoiditis were 29.7% and 32.4%, respectively[24].

Furthermore, the extent of the disease in each patient is not fixed over time. In this context, it is important to emphasize that in patients with proctitis or left colitis, the inflammatory process may progress to more proximal segments of the colon. This phenomenon may require greater clinical surveillance and even changes in the therapeutic regimen. In a study by Alkim *et al*[79], for example, the progression of inflammation to the more proximal segments of the colon occurred in 16.1% of patients with proctitis. The percentage was even higher in a study by Park *et al*[80], which showed that in 5 and 10 years, there was proximal progression in 44.7% and 60% of patients, respectively, with proctitis or left colitis.

The extent of UC influences the clinical course and prognosis of the disease. Patients with extensive colitis are more likely to be subjected to more intensive therapies or even colectomy[79,81]. In a retrospective study, Lee *et al*[82] demonstrated that the extent of disease is a factor that is independently associated with resistance to therapy with aminosalicylates (HR = 1:46; 95%CI: 1.01-2.10; P = 0.04). A Canadian study showed that left colitis (OR = 8.67; 95%CI: 1.79-41.87; $P < 0.001$) and extensive colitis (OR = 14.08; 95%CI: 3.12-63.60; $P < 0.001$) are also associated with more frequent usage of immunosuppressive drugs in patients with UC[83].

Whereas patients with proctitis do not seem to be at an increased risk of developing CRC compared with the general population, individuals with left or extensive colitis have a higher propensity to evolve this complication[84-87]. In a recent study, Manninen *et al*[85] concluded that patients with UC are at an increased risk of developing dysplasia and CRC compared with the general population (OR = 1.99; 95%CI: 1.14-3.25). The authors also noted that this risk is even higher in patients with extensive colitis (OR = 3.09; 95%CI: 1.5-5.75). Similar data were found in a recent meta-analysis, which described the risk of CRC in patients with UC as higher than in the general population (OR = 2.4; 95%CI: 2.1-2.7). Again, the risk was even higher in patients with extensive colitis (OR = 4.8; 95%CI: 3.9-5.9)[86]. The most recent data on the evolution of CRC risk over time are conflicting. Whereas certain authors have shown a tendency to stabilize the risk[88,89], Jess *et al*[90] showed a reduction in the period from 1979 to 2008. The authors suggested that this reduction occurred as a result of advances in therapeutic approaches to UC. Further studies are needed to evaluate the behavior of the risk of CRC in UC over time.

Disease activity

Clinical and laboratory characteristics that are consistent with greater disease activity at diagnosis have been shown to be important prognostic factors in patients with UC. The stratification of disease activity is important both in the choice of treatment modalities and in the assessment of prognosis. Lennard-Jones *et al*[91] evaluated 56 variables among patients with active UC in 181 hospital admissions. The authors concluded that fever, tachycardia, the number of evacuations and serum albumin level are important predictors of treatment failure and the need for colectomy. Those patients who had persistent fever and more than 8 stools per day in the first 24 h of hospitalization had a 4-5 times higher chance of becoming refractory to medical treatment and needing surgery. Carbonnel *et al*[92] evaluated factors associated with the failure of intravenous steroid therapy in hospitalized patients with active UC. The authors found that the risk of treatment failure was higher in patients meeting the criteria for severe disease in the classification of Truelove and Witts (RR = 2.26; 95%CI: 1.11-4.61). Lau *et al*[83] reported that more than 10 evacuations per day and the presence of blood in the stool at diagnosis were associated with greater usage of immunosuppression in patients with UC. Furthermore, Travis *et al*[93] concluded that patients with severe colitis who were hospitalized for more than 3 d and who persisted in having more than 8 stools per day and an elevated C-reactive protein level (> 45 mg/L) had a higher chance of colectomy. In a cohort study that evaluated the prognosis of patients during the first ten years of the disease, Solberg *et al*[72] concluded that anemia, an elevated erythrocyte sedimentation rate and fever at diagnosis were associated with a greater need for colectomy over time.

Endoscopic exams allow the direct evaluation of lesions of the intestinal mucosa in patients with UC. The severity of the lesions usually reflects clinical disease activity and may help to identify patients who are more likely to evolve worse disease behavior over time[92]. In a recent study, Canadian investigators found that the presence of moderate to severe endoscopic lesions was associated with an increased need for immunosuppression[83]. Carbonnel *et al*[94] demonstrated that patients admitted with active UC who had extensive and deep ulcerations (severe endoscopic activity) had a greater need for colectomy than did those with moderate endoscopic activity. Rutter *et al*[95] demonstrated that there is a close relationship of the degree of endoscopic activity (OR = 2.54; 95%CI: 1.45-4.44; P = 0.001) and histological activity (OR = 5.13; 95%CI: 2.36-11:14; $P < 0.001$) with the risk of developing CRC in patients with UC.

Several studies have considered fecal markers, and especially lactoferrin and calprotectin, as useful tools for the assessment of disease activity in UC and the response to treatment[96-98]. Recently, studies have shown that calprotectin and lactoferrin are also useful as predictors of clinical relapse in UC[99,100]. A study conducted by British investigators, who evaluated patients admitted with severe UC who needed intravenous corticosteroids, showed that a higher average concentration of fecal calprotectin was associated with an increased rate of colectomy[101].

Extraintestinal manifestations

The manifestations of UC may not be restricted to the colon and rectum. A variable percentage of patients may also have abnormalities in other organs and systems. Joint, skin, liver, eye and hematologic manifestations are common in patients with UC. Extraintestinal manifestations have been shown to be associated with a greater extent of disease and a worse prognosis[102]. Lakatos *et al*[103] conducted a study with 619 patients with UC who were followed for 25 years. The authors concluded that the presence of extraintestinal manifestations was associated with greater extent of disease. In the pediatric population, a recent study of Gower-Rousseau *et al*[104] concluded that the presence of extraintestinal manifestations in pediatric patients with UC increases the risk of colectomy (HR = 3.4; 95%CI: 1.2-10.0; $P = 0.02$).

Individuals with UC and primary sclerosing cholangitis (PSC) have a different phenotypic behavior compared to patients with UC only. In this group of patients, the presence of PSC is associated with increased occurrence of extensive colitis and CRC[105-107]. In a meta-analysis performed by Soetikno *et al*[108], the presence of PSC in patients with UC increased the risk of dysplasia and CRC (OR = 4.79; 95%CI: 3.58-6.41). Kornfeld *et al*[109] reported that the cumulative risk of individuals with UC and PSC to develop CRC was 25%, 33% and 40% at 10, 20 and 30 years from diagnosis of UC, respectively.

Serological markers

Anti-*Saccharomyces cerevisiae* antibody (ASCA) and perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA) were the first serological markers of IBD identified. The presence of a positive ASCA is more associated with CD, and p-ANCA is more associated with UC[110]. Over the past several years, however, these two serum markers not only became markers used to differentiate both IBD forms but also appeared to have prognostic implications. There is evidence that the presence of ASCA is associated with severe and refractory CD, whereas p-ANCA positivity in patients with UC seems to be associated with resistance to treatment[111,112]. This association has been reinforced by other recent publications. Ferrante *et al*[113] demonstrated that the usage of infliximab in patients with UC and p-ANCA+/ASCA- is more associated with a suboptimal early clinical response (OR = 0.40; 95%CI: 0.16-0.99; $P = 0.049$). In a study in a pediatric population with IBD, Dubinsky *et al*[114] concluded that the presence of a positive p-ANCA was independently associated with a primary non-response to anti-TNFα in UC patients.

Papp *et al*[115] found no association between ASCA, anti-laminaribioside carbohydrate antibody (ALCA), anti-chitobioside carbohydrate antibody (ACCA), anti-mannobioside carbohydrate antibody (AMCA) or anti-outer membrane porin C (anti-OmpC) and different phenotypes of UC.

There are only few studies on the role of antinuclear antibodies in UC. In a study in 97 patients with UC, Barahona-Garrido *et al*[116] concluded that the presence of antinuclear antibodies is associated with an increased risk of steroid dependency (OR = 3.9; 95%CI: 1.4-14.9; $P = 0.033$).

CONCLUSION

The global prevalence and incidence of UC have increased in recent decades. The increase in the number of new cases has been more evident in developing countries. Nevertheless, the mortality rate of UC has decreased over time, and currently, mortality in patients with UC is similar to or slightly higher than that in the general population. Environmental factors appear to be associated with the pathogenesis of UC. Among these factors, smoking and appendectomy have been considered protective against the development of UC. Moreover, evidence suggests that smoking and appendectomy are associated with less severe forms of UC and seem to confer protection against colectomy. Inversely, a greater extent of disease and higher disease activity are associated with a worse prognosis. Additionally, one should be attentive to the occurrence of nutritional deficiencies and extraintestinal manifestations, especially PSC, as well as to the presence of positive p-ANCA. The influence of age at diagnosis on the clinical course of UC is controversial, and therefore, further studies are needed to better evaluate this issue. Thus, based on current knowledge, it appears that demographic and clinical characteristics are useful to identify patients who tend to have more severe evolution of the disease. Earlier identification may allow more intensive therapeutic measures to be adopted earlier in the management of such patients.

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