



Epidemiology of Inflammatory Bowel Diseases (IBD) in Iran: A review of 740 patients in Fars province, Southern Iran

Seyed Alireza Taghavi¹, Ali Reza Safarpour^{2,*}, Seyed Vahid Hosseini^{2,3}, Hesameddin Noroozi⁵, Maral Safarpour⁴, Salar Rahimikazerooni²

¹Gastroenterohepatology Research Center, Nemazi hospital, Shiraz University of Medical Sciences, Shiraz, IR Iran

²Colorectal Research Center, Faghihi hospital, Shiraz University of Medical Sciences, Shiraz, IR Iran

³Laparoscopy Research Center, Faghihi hospital, Shiraz University of Medical Sciences, Shiraz, IR Iran

⁴Pharmacy school, International branch of Shiraz University of Medical Sciences, Shiraz, IR Iran

⁵Nutrition and Health school, Shiraz University of Medical Sciences, Shiraz, IR Iran

*Corresponding Author: Ali Reza Safarpour, Gastroenterohepatology Research Center, Shiraz University of Medical Sciences, Shiraz, IR Iran. Tel.: +98-7112357282, Fax: +98-7112307594, E-mail: asafarpour@sums.ac.ir

ABSTRACT

Background: Although the prevalence and incidence of Inflammatory Bowel Disease (IBD) are reaching a stable status in most of the industrialized countries, Asian countries have faced with an increasing number of IBD patients in the last two decades. However, due to the lack of national registry system, a limited amount of data is available on the epidemiology of IBD in Iran, particularly the southern parts of the country.

Objectives: The aim of this retrospective analytic study is clarification of multiple aspects of epidemiological factors of IBD patients in area of southern Iran.

Patients and Methods: Between 1989 and 2010, 740 patients with IBD, 620 ones with ulcerative colitis (UC) and 120 ones with Crohn's diseases (CD) were diagnosed as IBD cases and referred to our center. Then, their demographic characteristics, disease-related manifestations, complications, and their chief complaints were analyzed, retrospectively.

Results: The mean age at diagnosis was 34.68 ± 1.44 (range: 8–79 years) for UC patients and 32.97 ± 1.34 (range: 9–80 years) for CD ones. The male/female ratio was 0.9/1 and 0.98/1 for UC and CD patients, respectively. In comparison to rural patients, more urban ones with both UC and CD were registered (86.4% with UC and 91.74% with CD). No significant change was detected in onset-diagnosis lag time in IBD patients during the study. In this study, a significant positive relationship was found between the type of the disease and positive family history, $CD > UC$, ($\chi^2(6df) = 14.56$, $P = 0.024$). Furthermore, bloody diarrhea (69.4%) and abdominal pain (54.3%) were the most prevalent presentations in UC and CD patients, respectively. Besides, massive bleeding was the most prevalent complication for both UC and CD patients (32.9% and 19.8% respectively). In addition, 289 UC (46.6%) and 39 CD (33.7%) patients had experience at least one relapse during their course of disease. Nevertheless, no significant correlation was observed between the season of the onset and the type of the disease in UC and CD patients ($\chi^2(6df) = 6.09$, $P = 0.41$). Also, no significant relationship was detected between smoking and the type of disease ($\chi^2(2df) = 3.79$, $P = 0.13$).

Conclusions: An obvious increase in the number of IBD patients has been detected in our population during the past decades. This can be attributed to either improvement in the patients' and the physicians' knowledge and availability of diagnostic tools or a real increase in the incidence rate of the disease. In either case, this alarming increase should be taken into consideration by both the health authorities (regarding the significant burden) and the researchers of the field in our society.

Keywords: Inflammatory Bowel Diseases (IBD); Southern Iran; Epidemiology

Copyright © 2012, Kowsar Corp.; Published by Kowsar Corp.

► Article type: Research Article; Received: 26 Feb 2013, Revised: 03 Mar 2013, Accepted: 03 Apr 2012; DOI: 10.5812/acr.11477

► Implication for health policy/practice/research/medical education:

The Increase of IBD patients in Asian countries during past decades, is one of the most important medical issues in these countries. A multicenter, population based, large study must be done to clear all aspects of the diseases.

► Please cite this paper as:

Taghavi SA, Safarpour AR, Hoseini SV, Safarpour M, Noroozi H. Epidemiology of Inflammatory Bowel Diseases (IBD) in Iran: A review of 740 patients in Fars province, Southern Iran. *Annals of colorectal research journal*. *Ann Colorectal Res*: 2013;1(1): 17-22. DOI: 10.5812/acr.11477

► Copyright © 2012, Kowsar Corp.; Published by Kowsar Corp.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

1. Background

Inflammatory Bowel diseases (IBD), including Crohn's Disease (CD), Ulcerative Colitis (UC), and indeterminate colitis (IC), are multi-factorial diseases. Although both genetic and environmental factors are involved in the pathogenesis, the certain causes of these diseases are still unclear (1). Based on the recent epidemiologic data, IBD which was considered as a rare disease in many countries is turning to a global disease over time (2). Because of the low mortality rate associated with IBD, almost equal to normal population, the prevalence of the disease is also increasing along with its incidence (3). Although the prevalence and incidence of IBD are reaching a stable status in most of the industrialized countries (4), Asian countries have been faced with an increasing incidence of the disease in the last two decades. In the same line, the data from Japan (5), China (6), Hong-Kong (7), Singapore (8), India (9), Lebanon (10), and Kuwait (11) showed significant increase in IBD incidence in the recent years. Although the prevalence and incidence of IBD have not been properly studied in Iran, our country is located in the list of the countries with an increasing rate of IBD (12). Moreover, since the previous studies (13, 14) did not use the national registry system's data and were more hospital-based and retrospective, no clear epidemiological data is available on the prevalence of IBD in Iran. In fact, the review of the literature showed that hospital-based studies, especially for rare diseases, usually show a lower prevalence rate (15). The present retrospective descriptive-analytical study aims to clarify different demographic (especially for new cases in the past decades) and clinical characteristics of IBD patients in Fars province, South of Iran.

2. Objectives

The aim of this study is to clarify multiple aspects of epidemiological factors of IBD patients in area of southern Iran.

3. Patients and Methods

In the present study, we used the files of 744 patients diagnosed with IBD, which were collected during 21 years (1989-2010) in Gastroenterohepatology's IBD Registry between 1989 and 2009, Shiraz, Fars province, Iran. The data were collected through questionnaires containing the demographic data, signs and symptoms at the onset of the disease, date of the beginning of the disease, time interval between the onset of the disease and the date of diagnosis, and information regarding other clinical and surgical events. The questionnaires were completed by trained paramedical personnel for all the patients. IBD was diagnosed based on histological, clinical, endoscopic, and radiologic criteria determined by Lenard-jones (16). Each diagnosis was also confirmed by two gastroenterologists. Of course, in case the diagnosis changed

during the follow-up period (each follow-up period was 6 or 12 month during the study period), the final situation was considered for the patients. Relapse was defined as change in the patients' normal bowel habit accompanied with rectal bleeding with colonoscopic documentation. Because of the low number of the cases (only 4 patients), indeterminate colitis was excluded from this study. Extra Intestinal Disease was diagnosed based on the related specialists' opinions as well as the histological and laboratory data (if needed).

All the information was recorded in the patients' electronic files by trained staff. The subject and the objectives of the study were explained to all the patients and written informed consents were obtained from all the participants. This study was approved by the Ethic Committee of Shiraz University of Medical Sciences, Shiraz, Iran.

In the present study, Chi-square test was performed in order to determine the relationship between two categorical variables. Moreover, descriptive analysis of the data was done through the software, version 16 (Inc. Chicago, IL.). Also, P-value ≤ 0.05 was considered as statistically significant.

4. Results

According to the documentations, among the 783 patients whose information about the first time IBD diagnosis was registered in Gastroenterohepatology's IBD Registry between 1989 and 2009, 740 patients fulfilled the diagnostic criteria. In addition, the number of UC and CD patients were 620 (83.8%; Male: 297(47.9%), female: 323(52.1%) and 120 (16.2%; Male: 59(49.3%), female: 61(50.7%), respectively. The mean age at diagnosis was 34.68 ± 1.44 (range: 8 - 79 years) for UC patients and 32.97 ± 1.34 (range: 9 - 80 years) for CD patients. Moreover, the age range of 20-29 years was considered as the peak range in the related chart (Figure 1) and no second peak was detected. Furthermore, the male and female ratio was 0.9/1 and 0.98/1 for UC and CD patients, respectively. In addition, in comparison to rural patients, more urban ones had been registered for both UC (86.4%) and CD (91.7%). Among the UC patients, 4%, 81.6%, and 14.4% were uneducated, had under diploma degrees, and had university degrees, respectively. In CD patients, however, 1.7% was uneducated, 88.8% had under diploma degrees, and 9.5% had university degrees.

Moreover, 4.8% of UC and 5.1% of CD patients had positive family history of IBD in their first degree relatives. A positive significant correlation was also found between the type of the disease and positive family history which is more in CD than in UC, ($\chi^2(6df) = 14.56, P = 0.024$). In addition, bloody diarrhea (69.4%) and abdominal pain (54.3%) were the most prevalent presentations in UC and CD patients, respectively (Table 1). The frequency of arthritis, as the most prevalent Extra Intestinal manifestation was 8.2% and 12.1% among UC and CD patients respectively

(Table 2). Besides, after massive bleeding, which was the most prevalent complication for UC and CD patients (32.9% and 19.8%, respectively), toxic mega colon (2.9%) and fistula (10.3) were common complications in UC and CD patients, respectively (Table 3).

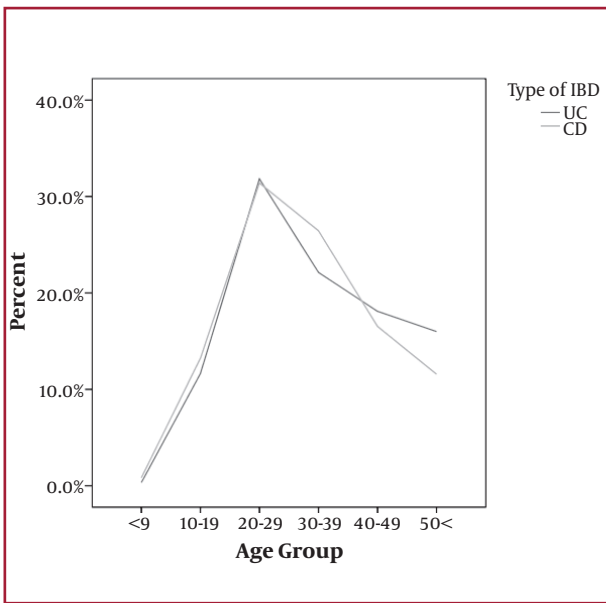


Figure 1. Age-specific distribution for UC and CD patients

Table 1. Frequency of symptoms at first presentation in IBD patients

Symptoms	Ulcerative colitis, %	Crohn's Disease, %
Bloody Diarrhea	69.4	47.4
Rectorrhagia	56	44
Abdominal pain	51.9	54.3
Constipation	19.2	16.4
Non – Bloody Diarrhea	9.4	13.8
Steatorrhea	8.4	6

Table 2. Extra Intestinal manifestations (EIMs) in IBD patients

EIMs	Ulcerative colitis, %	Crohn's Disease, %
Arthritis	8.2	12.1
Eye Involvement	5.0	7.8
Skin Involvement (EN, PG) ^a	5.3	9.5
Liver & Billiary Involvement	4.8	5.2
Total	23.3	34.6

^a Abbreviations: EN; Erythema Nodosum, PG; PyodermaGangranosum

Table 3. Frequency of complications in IBD patients

Complication	Ulcerative colitis (n = 620), No. (%)	Crohn's Disease (n = 120), No. (%)
Massive Bleeding	204(32.9)	23(19.8)
Toxic Mega colon	18(2.9)	2(1.7)
Fistula		12(10.3)
obstruction	8(1.3)	5(4.3)
Perforation	4(0.6)	
Stricture	1(0.2)	1(0.9)
Colorectal CA	7(1.1)	
Small Intestinal CA		
Protein losing EntroPathy	1(0.2)	
Total	243(39.2)	(43) 37

As shown in Table 4, the extent of the disease was analyzed by total colonoscopy in all IBD patients.

Table 4. Extension of the disease in IBD patients.

Disease	Pancolitis ^a , (%)	Proctitis ^b , (%)	Left sided colitis ^c , (%)	Small Intestine, (%)
UC (n = 620)	160(25.8)	152(24.5)	194(31.3)	
CD (n = 120)		2(1.7)		28(24.1)

^a Pancolitis: disease involved complete parts of colon

^b Proctitis: disease limited to rectum

^c Left sided colitis: disease below the splenic flexure

A total of 289 UC (46.6%) and 39 CD (33.7%) patients had experience at least one relapse during their course of disease. Analysis of the number of the new cases (according to their files, retrospectively) revealed an increase in the number of new IBD patients diagnosed each 10 years during the past three decades. In addition, Figures 2 and 3 reveal a five-fold increase in patients whose symptoms had appeared and IBD was diagnosed during 1970-2010.

In order to determine whether this annual increase was due to a real increase of new cases or an increased detection rate over time caused by improvement in diagnostic tools or more easier access to them, the lag time between the onset of the symptoms and the date of diagnosis was analyzed as an indirect indicator of "better" diagnosis. Nevertheless, comparison of years of diagnosis and onset-diagnosis lag times showed no significant changes in the lag times during the 30 years (Figures 2 and 3).

Furthermore, comparison of the mean onset-diagnosis lag time and the number of newly diagnosed IBD cases during 1970-2010 revealed a dramatic increase in cases, while it showed no decrease in the lag time (Figure 4).

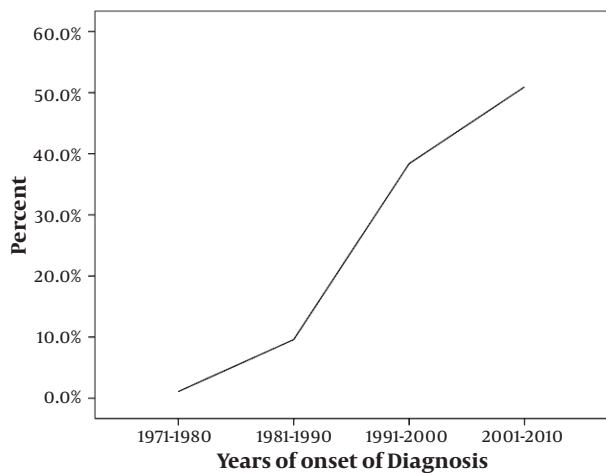


Figure 2. Dates of diagnosis in IBD patients

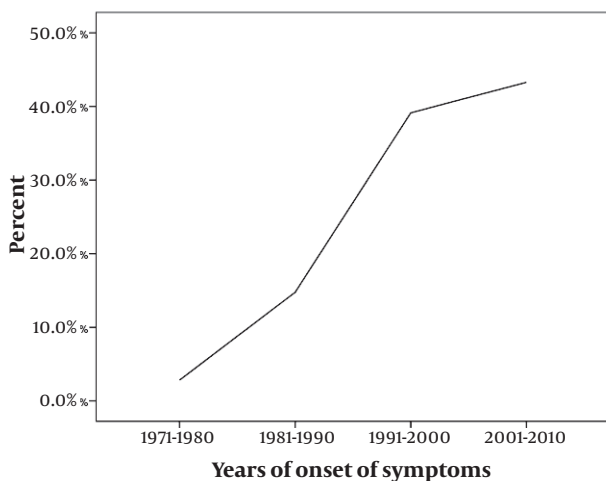


Figure 3. Dates of onset of symptoms in IBD patients

The Mean time interval between the onsets of the symptoms and the diagnosis time was 14.36 ± 13.1 months in the UC group and 16.56 ± 14.3 month in the CD group. Moreover, appendectomy rate was 2.9% (18 patients) and 7.6% (9 patients) in UC and CD patients, respectively. In addition, the frequency of tonsillectomy was 29 (4.7%) and 5 (4.1%) in UC and CD groups, respectively. UC patients mostly consumed 5ASA-preparations (71.7%) and corticosteroids (55.4%), while the most consumed drugs in the CD group were 5ASA-preparations (72.7%) and Infleximab

(57%). Other drugs which were consumed by both groups included Metotrexate, Antibiotics, and immunosuppressive medications (Azathioprine, 6-mercaptopurine). In this study, no significant relationship was found between the season of the onset and the type of the disease in UC and CD patients ($\chi^2(6df) = 6.09, P = 0.41$). Disease onset in spring, summer, autumn, and winter was 48.5%, 22%, 12.9%, and 6.16% for UC patients, and 47.8%, 26.1%, 8.7%, and 17.4% for CD patients. Besides, the disease onset in spring was more common for both UC and CD (Figure 5).

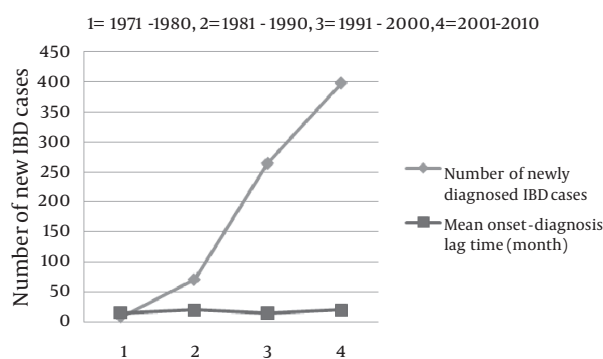


Figure 4. Comparison of mean onset-diagnosis lag time (month) with the number of newly diagnosed IBD cases between 1970 and 2010

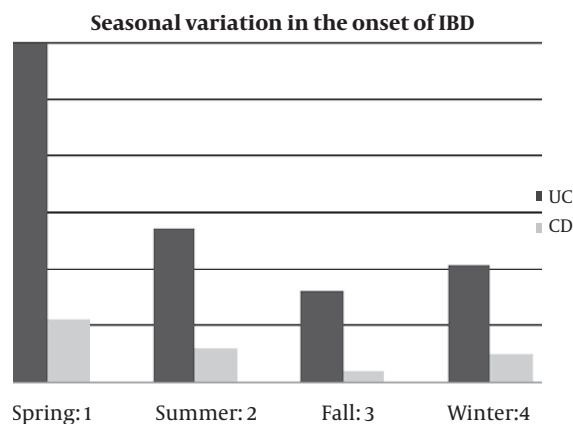


Figure 5. Seasonal variation in the onset of the symptoms in IBD patients (Spring: 1, summer: 2, Fall: 3, Winter: 4)

Finally, the frequency of smoking (cigarette and water pipe) was 5.2% (32) and 7.4% (9) in UC and CD patients, respectively. However, no significant correlation was detected between smoking and the type of the disease ($\chi^2(2df) = 3.79, P = 0.13$).

5. Discussion

Along with the significant increase of IBD all over the world, the results of the present study revealed increasing trends for both UC and CD in the past 3 decades in Iran (Figures 2 and 3). Moreover, an obvious increase has been observed in the new cases of IBD in the past three decades in our population. A portion of this increase may be due to the enhancement of the availability of the diagnostic services as well as an increase in the public knowledge regarding this type of disease. The present study showed no significant decrease in "lag time" between the onset of the symptoms and diagnosis in the study period. According to this finding, the increase of incidental cases is probably the main cause of the obvious increase of IBD patients in Iran. It is still not clear whether this increase in Iran and other Asian countries is due to the environmental factors emerging from industrialization or other unknown factors (2). The peak age at diagnosis in our study showed a pattern similar to other Asian countries, such as India (9) and Japan (17). In this pattern, only one peak at the age range of 20-40 was documented and no second peak (>62; 60 years old), usually observed in developed countries (18), was detected. On the other hand, two studies in South Korea (19) and Hong Kong (20) demonstrated small second peaks in their elderly population. In other studies conducted in Iran, the male/female ratio was reported to be 0.8/1 (13) and 0.7/1 (14) for UC and 1.4/1 (21) and 1.2/1 (22) for CD patients. In addition, the female predominance for UC in those studies was similar to the present one (0.9/1), it is in contrast to equal gender distribution in UC in other Asian countries (23-25). Regarding CD, the results of this study showed an equal sex distribution which was on the contrary to the male predominance reported in studies conducted in Hong Kong (20), Korea (19), and one other study performed in Iran (22). This may be related to a more health-conscious behavior in women, lead to a higher detection rate in this gender. In the present study, a positive significant relationship was found between the type of the disease (UC vs. CD) and family history of IBD. In two other Iranian studies (13, 14), the number of UC patients with a positive family history was more than that of the CD patients, which is in contrast to the findings of the present study (4.8% of UC and 5.1% of CD). Lower positive family history for UC patients in our study as well as Asian countries (1.6-4.5%) is in contrast with the results of the studies conducted in industrial countries (8-14%) (26, 27). In similar studies in Singapore (8) and South Korea (28), the percent of familial occurrence for CD was 0-3% which is lower than our study results (5.1%).

In our study, diarrhea (mostly bloody) for UC and abdominal pain for CD patients were the most prevalent presentations at the onset of the disease. Despite the similarity between our results and two other studies conducted on CD in Iran (13, 14), a clear difference was

observed between Iranian (14) and other Asian (29) UC patients regarding their first complaint (Diarrhea vs. rectal bleeding). Along with other similar studies conducted in Iran (14, 22) and Kuwait (11), arthritis was the most prevalent extra-intestinal manifestation (EIMs) for both UC (18.2%) and CD patients (12.1%) in the present study, as well. Furthermore, the frequency of other EIMs in our study as well as other Iranian (30), Indian (31), and Chinese (6) studies was reported as 8-16%. Only in one study performed in Iran, EIMs was reported above 60% for both CD and UC (22). It is possible that the lower rate of EIM in Iran and other Asian countries might be due to the lack of long time cohort studies rather than a real difference. Left sided colitis was the most prevalent (31.3%) colon-related disorder in our study and one other Iranian report (22). Other Iranian reports, however, reported proctitis as the most prevalent colonic involvement (13, 14). Most studies conducted in Asian countries have shown a high rate of left sided colitis among the UC patients. The prevalence of this form of colonic extension in China (6) and Korea (25) was reported as 92.7% and 35.1%, respectively. However, pancolitis, with the prevalence rate of 37.6%, was shown as the most prevalent type in Singapore (32). Along with the results of a study conducted in Netherland (33), the findings of the present study revealed no relationship between the seasons and the onset of IBD. This is in contrast with a report from Norway showed a significant peak in the onset of UC during December ($\chi^2(1df) = 21.6, P = 0.028$); however, no seasonal variation was detected in CD (34). It is well accepted that cigarette smoking is protective against UC and probably a risk factor for CD (35, 36). However, no significant correlation was found between smoking (cigarette or water pipe) and IBD in the present study. Malekzadeh et al. also showed no significant correlation between CD and smoking, but confirmed the protective effect of cigarette smoking against UC (36). The retrospective nature of data collection for a portion of our population and incomplete cooperation of the private practices are the limitations of this study and should be considered in future. On the other hand, the large study population was one of the advantages of this study. Finally, it can be concluded that a significantly increased rate of IBD either due to the people's and the physicians' knowledge improvement and newer diagnostic tools or a real increase in the incidence rate is well documented in our population and should serve as a focus for the health authorities as well as the researchers of this field.

Acknowledgements

The authors would like to thank Gastroenterohepatology and Colorectal research centers for their cooperation in the process of data collection. Research Improvement Center of Shiraz University of Medical Sciences and Ms. Afsaneh Keivanshekouh are also appreciated for improving the use of English in the manuscript.

Authors' Contribution

Main idea was proposed by Seyed Alireza Taghavi, Ali Reza Safarpour and Seyed Vahid Hoseini. Study design and writing was done by Ali Reza Safarpour, Seyed Alireza Taghavi, Maral Safarpour and Hesameddin Noroozi. Data collecting was done by Maral Safarpour, Hesameddin Noroozi and Salar Rahimikazerooni. Data Analysis was done by Ali Reza Safarpour and Hesameddin Noroozi.

Financial Disclosure

None declared.

Funding/Support

None declared.

References

- Podolsky DK. Inflammatory bowel disease. *N Engl J Med*. 2002;**347**(6):417-29.
- Molodecky Natalie A, Soon Ing Shian, Rabi Doreen M, Ghali William A, Ferris Mollie, Chernoff Greg, et al. Increasing Incidence and Prevalence of the Inflammatory Bowel Diseases With Time, Based on Systematic Review. *Gastroenterology*. 2012;**142**(1):46-54.e+43.
- Bernstein CN, Blanchard JF, Rawsthorne P, Wajda A. Epidemiology of Crohn's disease and ulcerative colitis in a central Canadian province: a population-based study. *Am J Epidemiol*. 1999;**149**(10):916-24.
- Lakatos PL. Recent trends in the epidemiology of inflammatory bowel diseases: up or down? *World J Gastroenterol*. 2006;**12**(38):6102-8.
- Fujimoto T, Kato J, Nasu J, Kuriyama M, Okada H, Yamamoto H, 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**(3):229-35.
- Jiang Xue-Liang, Cui Hui-Fei. An analysis of 10218 ulcerative colitis cases in China. *World Journal Of Gastroenterology: WJG*. 2002;**8**(1):158-61.
- Lok KH, Hung HG, Ng CH, Kwong KC, Yip WM, Lau SF, et al. Epidemiology and clinical characteristics of ulcerative colitis in Chinese population: experience from a single center in Hong Kong. *J Gastroenterol Hepatol*. 2008;**23**(3):406-10.
- Thia KT, Luman W, Jin OC. Crohn's disease runs a more aggressive course in young Asian patients. *Inflamm Bowel Dis*. 2006;**12**(1):57-61.
- Sood A, Midha V, Sood N, Bhatia AS, Avasthi G. Incidence and prevalence of ulcerative colitis in Punjab, North India. *Gut*. 2003;**52**(11):1587-90.
- Abdul-Baki H, ElHajj I, El-Zahabi LM, Azar C, Aoun E, Zantout H, et al. Clinical epidemiology of inflammatory bowel disease in Lebanon. *Inflamm Bowel Dis*. 2007;**13**(4):475-80.
- Al-Shamali MA, Kalaoui M, Patty I, Hasan F, Khajah A, Al-Nakib B. Ulcerative colitis in Kuwait: a review of 90 cases. *Digestion*. Switzerland: Karger AG, Basel; 2003. p. 218-24.
- Cosnes J, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and Natural History of Inflammatory Bowel Diseases. *Gastroenterology*. 2011;**140**(6):1785-94.
- Aghazadeh R, Zali MR, Bahari A, Amin K, Ghahghaie F, Firouzi F. Inflammatory bowel disease in Iran: a review of 457 cases. *J Gastroenterol Hepatol*. 2005;**20**(11):1691-5.
- Vahedi H, Merat S, Momtahan S, Olfati G, Kazzazi AS, Tabrizian T, et al. Epidemiologic characteristics of 500 patients with inflammatory bowel disease in Iran studied from 2004 through 2007. *Arch Iran Med*. Iran: 2009. p. 454-60.
- Farrokhyar F, Swarbrick ET, Irvine EJ. A critical review of epidemiological studies in inflammatory bowel disease. *Scand J Gastroenterol*. 2001;**36**(1):2-15.
- Lennard-Jones JE. Classification of inflammatory bowel disease. *Scand J Gastroenterol Suppl*. 1989;**170**:2-6.
- Morita N, Toki S, Hirohashi T, Minoda T, Ogawa K, Kono S, et al. Incidence and prevalence of inflammatory bowel disease in Japan: nationwide epidemiological survey during the year 1991. *J Gastroenterol*. 1995;**30** Suppl 8:1-4.
- Loftus EV, Jr, Sandborn WJ. Epidemiology of inflammatory bowel disease. *Gastroenterol Clin North Am*. 2002;**31**(1):1-20.
- Yang SK, Yun S, Kim JH, Park JY, Kim HY, Kim YH, et al. Epidemiology of inflammatory bowel disease in the Songpa-Kangdong district, Seoul, Korea, 1986-2005: a KASID study. *Inflamm Bowel Dis*. 2008;**14**(4):542-9.
- Leong RW, Lau JY, Sung JJ. The epidemiology and phenotype of Crohn's disease in the Chinese population. *Inflamm Bowel Dis*. 2004;**10**(5):646-51.
- Fallahi GH, Moazzami K, Tabatabaeiyan M, Zamani MM, Asgar-Shirazi M, Najafi M, et al. Clinical characteristics of Iranian pediatric patients with inflammatory bowel disease. *Acta Gastroenterol Belg*. 2009;**72**(2):230-4.
- Derakhshan F, Naderi N, Farnood A, Firouzi F, Habibi M, Rezvany MR, et al. Frequency of three common mutations of CARD15/NOD2 gene in Iranian IBD patients. *Indian J Gastroenterol*. 2008;**27**(1):8-11.
- Yoshida Y, Murata Y. Inflammatory bowel disease in Japan: studies of epidemiology and etiopathogenesis. *Med Clin North Am*. 1990;**74**(1):67-90.
- Duphare H, Misra SC, Patnaik PK, Mathur M, Tandon RK. Spectrum of ulcerative colitis in north India. *J Clin Gastroenterol*. 1994;**18**(1):23-6.
- Yang SK, Hong WS, Min YI, Kim HY, Yoo JY, Rhee PL, et al. Incidence and prevalence of ulcerative colitis in the Songpa-Kangdong District, Seoul, Korea, 1986-1997. *J Gastroenterol Hepatol*. 2000;**15**(9):1037-42.
- Monsen U, Brostrom O, Nordenvall B, Sorstad J, Hellers G. Prevalence of inflammatory bowel disease among relatives of patients with ulcerative colitis. *Scand J Gastroenterol*. 1987;**22**(2):214-8.
- Yang H, McElree C, Roth MP, Shanahan F, Targan SR, Rotter JJ. Familial empirical risks for inflammatory bowel disease: differences between Jews and non-Jews. *Gut*. 1993;**34**(4):517-24.
- Park JB, Yang SK, Byeon JS, Park ER, Moon G, Myung SJ, et al. Familial occurrence of inflammatory bowel disease in Korea. *Inflamm Bowel Dis*. 2006;**12**(12):1146-51.
- Park SH, Kim YM, Yang SK, Kim SH, Byeon JS, Myung SJ, et al. Clinical features and natural history of ulcerative colitis in Korea. *Inflamm Bowel Dis*. 2007;**13**(3):278-83.
- Mir-Madjlessi SH, Forouzandeh B, Ghadimi R. Ulcerative colitis in Iran: a review of 112 cases. *Am J Gastroenterol*. 1985;**80**(11):862-6.
- Pokharna RK, Kabra PK, Sharma R, Kochar DK. Extraintestinal manifestations of idiopathic ulcerative colitis in northwestern India. *Indian J Gastroenterol*. 2004;**23**(3):89-90.
- Ling KL, Ooi CJ, Luman W, Cheong WK, Choen FS, Ng HS. Clinical characteristics of ulcerative colitis in Singapore, a multiracial city-state. *J Clin Gastroenterol*. 2002;**35**(2):144-8.
- Romberg-Camps MJ, Hesselink-van de Kruijs MA, Schouten LJ, Dagnelie PC, Limonard CB, Kester AD, et al. Inflammatory Bowel Disease in South Limburg (the Netherlands) 1991-2002: Incidence, diagnostic delay, and seasonal variations in onset of symptoms. *J Crohns Colitis*. 2009;**3**(2):115-24.
- Moum B, Aadland E, Ekbohm A, Vatn MH. Seasonal variations in the onset of ulcerative colitis. *Gut*. 1996;**38**(3):376-8.
- Ekbohm A. The epidemiology of IBD: a lot of data but little knowledge. How shall we proceed? *Inflamm Bowel Dis*. 2004;**10** Suppl 1:S32-4.
- Malekzadeh F, Alberti C, Nouraei M, Vahedi H, Zaccaria I, Meinzer U, et al. Crohn's disease and early exposure to domestic refrigeration. *PLoS One*. 2009;**4**(1).