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Assessment of health-related quality of life of Iraqi patients with inflammatory bowel disease

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ABSTRACT

Assessment of health-related quality of life among Iraqi inflammatory bowel disease patients as well as assess the effects of socio-demographic and clinical variables on health-related quality of life. The current cross-sectional study was carried out on 150 patients already diagnosed with inflammatory bowel disease who attended the Gastrointestinal and Hepatology Teaching Hospital/Medical City/Baghdad. The mean age of the patients was (31.7 ± 11.4 years), the number of Crohn's disease patients was 76 while the number of ulcerative colitis patients was 74. Total health-related quality of life score was significantly higher in Crohn's disease compared to ulcerative colitis. Regarding the components of health-related quality of life: only bowel score was significantly higher in Crohn's disease compared to ulcerative colitis. For all patients, higher education levels, out-patient management, and a higher number of infliximab doses received predict the high health-related quality of life (direct correlation). For ulcerative colitis patients, patients received treatment in an outpatient setting, and a higher number of infliximab doses predict the high health-related quality of life (direct correlation). For Crohn's disease patients, in univariate analysis; patients received treatment in an outpatient setting, predict the high health-related quality of life (direct correlation), while a higher number of chronic drugs inversely correlate with health-related quality of life. Health-related quality of life total score and the bowel score were significantly higher in CD compared to UC. For all patients, higher education levels, out-patient management, and a higher number of infliximab doses received predict elevated HRQOL.

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INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic inflammatory diseases of the gastrointestinal tract, which include both Crohn's disease (CD) and ulcerative colitis (UC) (Saadah, 2011). The etiology of IBD is a multifactorial entity with both genetic susceptibility and environment-related factors contributing to the disease process (Lakatos *et al.*, 2006). Globally, the incidence of IBD varies from - 24.5 per 100,000 person-years (Lakatos, 2006). Management of IBD can involve medica- tions, dietary modifications, as well as surgery, ac- cording to the severity of the disease and response to therapy (Lakatos, 2009). Health-related quality

of life (HRQOL) adapted from the broader and general concept quality of life (QOL). Health-related quality of life can define as: "The extent to which one's usual or expected physical, emotional and social well-being are affected by a medical condition or its treatment" (Cella, 1995). The life expectancy of patients with IBD is usually normal (Ekbom *et al.,* 1992); however, the relapsing nature and the early onset of the disease have significant psychological, social, and financial impacts (Ross *et al.,* 2011, Pallis, 2002). Many studies have investigated the HRQOL in IBD and showed that IBD patients have HRQOL with social, physical, and emotional dysfunction (Martin *et al.,* 1995, Graff *et al.,* 2006). The current study aimed to assess HRQOL among Iraqi inflammatory bowel disease patients as well as assess the effects of socio-demographic and clinical variables on HRQOL.

Patients and methods

The current cross-sectional study was carried out on 150 already diagnosed IBD patients attending the "Gastroenterology and Hepatology Teaching Hospital/Medical City/Baghdad" from September 2017 to January 2018. The number of UC patients was 74 while the number of CD patients was 76.

Inclusion criteria

1. IBP patients with disease duration of 6 months or more, aged 18 years or more of either sex.
2. Patients should have good communication and willing to participate in the study.

Exclusion criteria

1. Patient with impairment in speech, hearing, or cognition.
2. Patient being on treatment for any psychological, or neurological diseases.
3. Patients are providing incomplete information.

Sample Size Calculation Population

The sample size calculated by using Raosoft sample size calculator. Assuming the margin of error of 5% and the confidence level is 95%, the total number of IBD patients registered at the above hospital was 193 patients (who aged above 18 years) at the beginning of the current study then the sample size will be at least 131 patients.

The questionnaires

The quality of life assessed by using the Arabic version of Short Inflammatory Bowel Disease Questionnaire (SIBDQ) (Jowett *et al.,* 2001). SIBDQ is a disease-specific, validated and reliable tool for measuring HRQOL in adult patients with IBD and contains ten questions (Jowett *et al.,* 2001). For each of the ten question, the response graded on a 7-point Likert scale ranged from 1 (worst aspect) to 7 (best aspect). The total scores range from 10-70, with higher scores indicating better HRQOL (Mahalli and Alharthi, 2017).

Four HRQOL domains (systemic, social, bowel, and emotional) calculated and scored. The bowel domain (summation of the responses to Q4, Q6 and Q9), the social domain (sum of the responses to Q2 and Q3), the systemic domain (sum of the responses to Q1 and Q7), and the emotional domain (sum of the responses to Q5,Q8 and Q10). Finally, the total score of SIBDQ was composed of the sum of the responses to all ten questions (Mahalli and Alharthi, 2017).

Study design

The pilot study

A pilot study was carried out on 10 IBD patients to test and optimize the Arabic words of the questionnaires used in this study, the data obtained from the pilot study excluded from the major study.

Administration of questionnaires

The researcher herself collected the data. When the patients reached the hospital to for their scheduled dose of the biological agent, they were asked to participate in the study, if they accepted, a complete explanation of the questionnaire done. Each patient spent about 5 minutes to fill out the questionnaire completely.

Statistical analysis

Two samples t-test used to analyze the differences in means between two groups (if both follow a normal distribution with no significant outlier). Discrete variables presented using there number and percentage, chi-square test used to analyze the discrete variable. Binary logistic regression analysis was used to calculate the odds ratio (OR) and their 95% confidence intervals. Linear regression analysis performed to assess the relationship between different variables if one or both of them follow normal distribution person regression used but if both did not follow normal distribution spearman correlation will be used. The negative sign indicates an inverse relationship, but a positive sign represents the direct relationship. Statistical Package for the Social Sciences SPSS (Chicago, IL) version 20.0.0 was used to make the statistical analysis, p-value considered to be significant if less than 0.05.

RESULTS

The socio-demographic and disease characteristics for all patients shown in table 1.

Table 1: Socio-demographic and disease characteristics for all patients

Socio-demographic		Disease characteristics	
Variables	Value	Variables	Value
Age (years), mean ± SD (range)	31.7 ± 11.4 (18 – 60)	Disease duration (years), mean ± SD (range)	5.0 ± 4.4 (0.5 – 26.0)
<20 years	21 (14.0%)	Disease type, no. (%)	
20 – 29 years	54 (36.0%)	Ulcerative colitis	74 (49.3%)
30 – 39 years	41 (27.3%)	Crohn's disease	76 (50.7%)
40 – 49 years	19 (12.7%)	Disease activity, no. (%)	
50 – 60 years	15 (10.0%)	Remission	103 (68.7%)
Gender, no. (%)		Active	47 (31.3%)
Female	64 (42.7%)	Surgical treatment, no. (%)	25 (16.7%)
Male	86 (57.3%)	The number of chronic drugs, no. (%)	
Social status, no. (%)		Single medication	63 (42%)
Single	71 (47.3%)	Multiple medications	87 (58%)
Married	79 (52.7%)	The Number of chronic diseases, no. (%)	
Education level, no. (%)		No disease	142 (94.7%)
Illiterate	2 (1.3%)	Single disease	6 (4%)
Primary	30 (20.0%)	Multiple diseases	2 (1.3%)
Secondary	55 (36.7%)	Admission, no. (%)	
College	63 (42.0%)	In-patients	22 (14.7%)
Residence, no. (%)		Out-patients	128 (85.3%)
Urban	129 (86%)	Number of infliximab doses of, mean ± SD (range)	7.55 ± 6.45 (1 – 31)
Rural	21 (14%)	Disease duration (years), mean ± SD (range)	5.0 ± 4.4 (0.5 – 26.0)
Smoking, no. (%)	14 (9.3%)		
Drinker, no. (%)	1 (0.7%)		

Table 2: Total HRQOL score with its sub-scores for all patients

Variables	Value
Systemic, mean ± SD (range)	7.89 ± 3.29 (2 - 14)
Social, mean ± SD (range)	8.42 ± 3.45 (2 - 14)
Bowel, mean ± SD (range)	12.95 ± 4.96 (3 - 21)
Emotional, mean ± SD (range)	10.49 ± 4.63 (3 - 19)
Total score, mean ± SD (range)	39.74 ± 12.67 (14 - 63)

The total HRQOL score with its sub-scores for all patients are shown in table 2 and figures 1. Quality of life score was significantly higher in CD compared to UC. Regarding the components of QOL: only bowel score was significantly higher in CD compared to UC (table 3, figure 2). For all patients, in univariate analysis; higher education levels, outpatient management, and a higher number of infliximab doses received predict elevated HRQOL (direct correlation). In multivariate analysis, the only place of management and number of infliximab doses independently correlate with HRQOL, as illustrated in table 4. For UC patients, in univariate analysis; patients received treatment in an outpatient setting, and a higher number of infliximab doses predicts elevated HRQOL (direct correlation). In multivariate analysis, the only place of management independently correlates with HRQOL, as illustrated in table 5. For CD patients, in univariate analysis; patients received treatment in an outpatient setting, predict elevated HRQOL (direct correlation), while a higher number of chronic drugs inversely correlate with HRQOL. In multivariate analysis, the only place of management independently correlates with HRQOL, as illustrated in table 6.

DISCUSSION

Inflammatory bowel diseases (IBD) with the two main subtypes, Crohn's disease (CD) and ulcerative colitis (UC), are chronic relapsing inflammatory disorders of the gastrointestinal tract (Vavricka *et al.,* 2017). It has been a worldwide health-care problem with a continually increasing incidence (Zhang and Li, 2014). The relationship between socio-demographic and disease characteristics and HRQOL has investigated. The results of the present study showed that the mean age of patients was

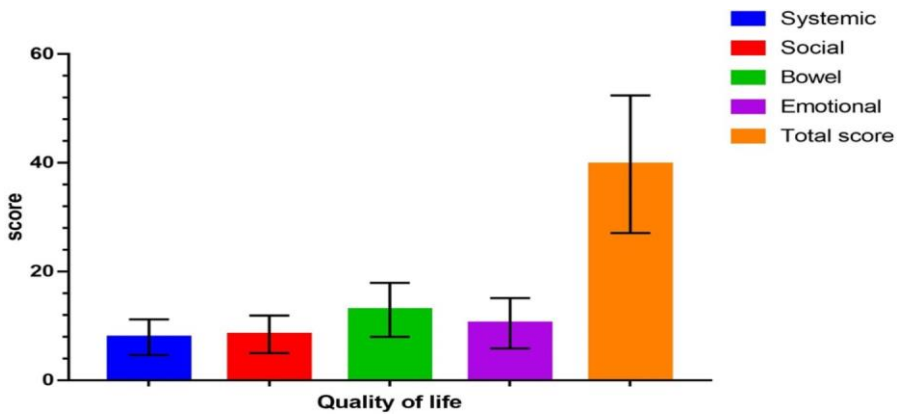

Figure 1: HRQOL for all patients

Table 3: Total HRQOL score with its sub-scores for each disease

Variables	Ulcerative colitis	Crohn's disease	p-value
Number	74	76	-
Systemic, mean ± SD	7.72 ± 3.14	8.05 ± 3.44	0.533[a]
Social, mean ± SD	7.89 ± 3.07	8.93 ± 3.74	0.064[a]
Bowel, mean ± SD	11.81 ± 4.85	14.05 ± 4.85	0.005[a]
Emotional, mean ± SD	9.93 ± 4.67	11.03 ± 4.56	0.149[a]
Total score, mean ± SD	37.35 ± 11.86	42.07 ± 13.08	0.022[a]

[a]: independent t-test, [b]: chi-square test

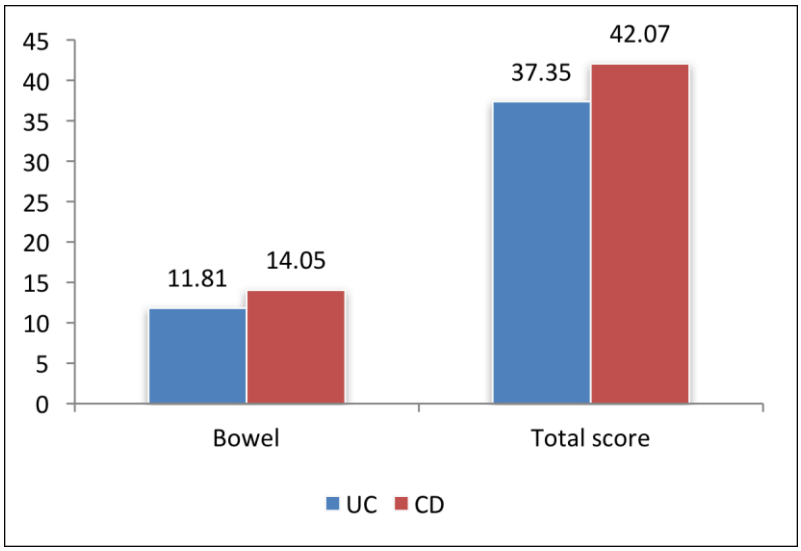

Figure 2: Total HRQOL and bowel component scores of UC and CD

(31.7 ± 11.4 years). Some other studies came with the proximate result regarding the mean age of IBD patients. In which mean age of a sample of IBD patients was 32.6 ± 12.3 years in a study done in Kuwait by(Khaled Al-Jarallah *et al.,* 2012) (Al-Jarallah *et al.,* 2013). Most CD and UC studies showed peak incidence in the second to the fourth decade (Ko *et al.,* 2014). The percentage of male patients was 57.3 %, while the percentage of female patients was 42.7%, this result approximate to Iranian study (Masnadi Shirazi *et al.,* 2013) which showed that percentage of male patients was 53%, while the percentage of female patients was 47% (Shirazi *et al.,* 2013). The overall sex differences for IBD are inconsistent, suggesting gender-specific risk factors may not exist (Ko *et al.,* 2014), the majority of patients (42%) had college education level, and 36.7% had secondary education, this result similar to a Saudi study (El. Mahalli and Alharthi 2016) which showed that patients with (secondary school and more) represented 78% of all patients (Mahalli and Alharthi, 2017).

In this study 86% of total patients live in urban areas, and only 14% live in a rural area ,and this result compatible with a study by R Aghazadeh *et al.,* (2005 Tehran, Iran) where the vast majority of studied patients have been residing in urban areas (Aghazadeh *et al.,* 2005), this variation may be due to that urbanisation of societies, associated with changes in diet, antibiotic use, hygiene status,

Table 4: Uni- and multivariate linear regression analysis between HRQOL and other variables for all patients

Variables	Univariate analysis		Multivariate analysis	
	r	P-value	r	P-value
Gender	0.138	0.092	0.147	0.079
Age	-0.026	0.749	-	-
Disease duration	-0.088	0.283	-	-
Social status (married)	-0.112	0.174	-	-
Education level	0.194	0.017	0.087	0.297
Location (rural)	-0.061	0.458	-	-
Smoking	0.040	0.629	-	-
Surgical Treatment	-0.035	0.668	-	-
Number of drugs used	-0.144	0.079	-	-
Number of chronic diseases	-0.098	0.234	-	-
Place of management (out-patients)	0.335	<0.001	0.333	<0.001
Number of infliximab doses	0.223	0.006	0.194	0.020

R^2 = 0.246, p-value < 0.001; For univariate analysis, Spearman regression used, for multivariate analysis linear regression with dummy variables used with partial correlation coefficient used for presenting the relationship.

Table 5: Uni- and multivariate linear regression analysis between HRQOL L and other variables for UC patients

Variables	Univariate analysis		Multivariate analysis	
	r	P-value	r	P-value
Gender	0.120	0.308	-	-
Age	0.222	0.058	0.172	0.156
Disease duration	-0.005	0.968	-	-
Social status (married)	0.095	0.422	-	-
Education level	0.138	0.239	-	-
Location (rural)	-0.030	0.800	-	-
Smoking	0.095	0.422	-	-
Surgical Treatment	-0.169	0.149	-	-
Number of drugs used	0.013	0.911	-	-
Number of chronic diseases	0.011	0.924	-	-
Place of management (out-patients)	0.353	0.002	0.337	0.004
Number of infliximab doses	0.238	0.041	0.217	0.071

R^2 = 0.287, p-value < 0.001; For univariate analysis, Spearman regression used, for multivariate analysis linear regression with dummy variables used with partial correlation coefficient used for presenting the relationship.

microbial exposures and pollution have been implicated as potential environmental risk factors for IBD (Ng *et al.,* 2013).

Measuring HRQOL provides important data to quantify the impact of disease on the daily life of patients (Mahalli and Alharthi, 2017). Inflammatory bowel disease (IBD) has a significant negative impact on HRQOL (Ueno *et al.,* 2017). In the present study, the HRQOL score was significantly higher in CD compared to UC. Regarding the components of HRQOL: only bowel score was significantly higher in CD compared to UC. That mean patients with CD have less abdominal pain, less problem in passing gases and less need to go to the bathroom (Q4, Q6, and Q9) that explain the cause of higher HRQOL in CD patients than UC patients.

For all patients, in univariate analysis; higher education levels predict elevated HRQOL (direct correlation). Other studies came with the similar result (Mahalli and Alharthi, 2017). This is because educated patients may have more chance to read more about the disease and learn how to cope with frequent relapses. Moreover, educated patients may show higher adherence to treatment therapy. Education results in less in-patient care, fewer visits to primary care physicians, improved treatment adherence, and enhanced quality of life (Mahalli and Alharthi, 2017). In multivariate analysis, the only place of management and number of Infliximab doses independently correlate with HRQOL (independent or good predictors), according to the place of management, the outpatient setting associated with good HRQOL. Many other studies show that inpatient setting associated with lower scores of HRQOL (Moradkhani *et al.,* 2013), and then surely

Table 6: Uni-and multivariate linear regression analysis between HRQOL and other variables for CD patients

Variables	Univariate analysis		Multivariate analysis	
	r	P-value	r	P-value
Gender	0.119	0.308	-	-
Age	-0.189	0.102	-	-
Disease duration	-0.109	0.347	-	-
Social status (married)	-0.225	0.051	-	-
Education level	0.210	0.069	-	-
Location (rural)	-0.016	0.893	-	-
Smoking	-0.037	0.753	-	-
Surgical Treatment	-0.042	0.721	-	-
Number of drugs used	-0.313	0.006	0.078	0.519
Number of chronic diseases	-0.180	0.119	-	-
Place of management (out-patients)	0.253	0.027	0.235	0.049
Number of infliximab doses	0.183	0.114	-	-

R^2 = 0.287, p-value < 0.001; For univariate analysis, Spearman regression used, for multivariate analysis linear regression with dummy variables used with partial correlation coefficient used for presenting the relationship.

Outpatients will have good HRQOL. According to some Infliximab doses which independently correlate with HRQOL, this result came similar to other studies (Vogelaar *et al.,* 2009) which showed that tumour necrosis factor (TNF)-α inhibitors report a positive impact on HRQOL and TNF-α inhibitors improved HRQOL compared to placebo (Vogelaar *et al.,* 2009). Other studies also showed that effective treatments associated with a normalization in quality of life, both for CD and for UC; this has demonstrated for conventional drugs such as immunosuppressives, and biological agents (Rocchi *et al.,* 2012), but this result came opposite to another study (M. Kalafateli *et al.,* 2013) which showed that patients with UC using anti-TNF-α agents had a worse QoL HRQOL compared to non-users (Kalafateli *et al.,* 2013).

In the present study in CD patients, higher number of chronic drugs inversely correlate with HRQOL and this may be due to that higher number of chronic medications may decrease the adherence to treatment, poor treatment adherence may result in more frequent relapses and a disabling disease course and this will lead to a decrease in HRQOL (Jaghult *et al.,* 2011).

CONCLUSIONS

Health-related quality of life total score and the bowel score were significantly higher in CD compared to UC. For all patients, higher education levels, out-patient management, and a higher number of infliximab doses received predict elevated HRQOL (direct correlation).

Conflict of interests

No financial, personal, or any other type of interest will present a conflict concerning this work.

Author contributions

Nisreen Jumaah Jebur; conception and design, and acquisition of data, writing the initial and final version of the article, Dheyaa J. Kadhim: conception and design, critical revision, final approval, Nawal. M. Farhan: critical revision, final approval, Hayder A Fawzi: analysis and interpretation of data,

REFERENCES

Raosoft sample size calculator [Online]. Available: http://www.raosoft.com/samplesize.html [Accessed].

Aghazadeh, R., Zali, M. R., Bahari, A., Amin, K., Ghahghaie, F. & Firouzi, F. 2005. Inflammatory bowel disease in Iran: a review of 457 cases. *J Gastroenterol Hepatol,* 20**,** 1691-5.

Al-Jarallah, K., Shehab, D., Al-Azmi, W. & Al-Fadli, A. 2013. Rheumatic complications of inflammatory bowel disease among Arabs: a hospital-based study in Kuwait. *International journal of rheumatic diseases,* 16**,** 134-138.

Cella, D. F. 1995. Measuring quality of life in palliative care. *Semin Oncol,* 22**,** 73-81.

Ekbom, A., Helmick, C. G., Zack, M., Holmberg, L. & Adami, H. O. 1992. Survival and causes of death in patients with inflammatory bowel disease: a population-based study. *Gastroenterology,* 103**,** 954-60.

Graff, L. A., Walker, J. R., Lix, L., Clara, I., Rawsthorne, P., Rogala, L., Miller, N., Jakul, L., Mcphail, C., Ediger, J. & Bernstein, C. N. 2006. The relationship of inflammatory bowel disease type and activity to psychological functioning and quality of life. *Clin Gastroenterol Hepatol,* 4**,** 1491-1501.

Jaghult, S., Saboonchi, F., Johansson, U. B., Wredling, R. & Kapraali, M. 2011. Identifying predictors of low health-related quality of life among patients with inflammatory bowel disease: comparison between Crohn's disease and ulcerative colitis with disease duration. *J Clin Nurs,* 20**,** 1578-87.

Jowett, S. L., Seal, C. J., Barton, J. R. & Welfare, M. R. 2001. The short inflammatory bowel disease questionnaire is reliable and responsive to a clinically important change in ulcerative colitis. *Am J Gastroenterol,* 96**,** 2921-8.

Kalafateli, M., Triantos, C., Theocharis, G., Giannakopoulou, D., Koutroumpakis, E., Chronis, A., Sapountzis, A., Margaritis, V., Thomopoulos, K. & Nikolopoulou, V. 2013. Health-related quality of life in patients with inflammatory bowel disease: a single-center experience. *Annals of Gastroenterology: Quarterly Publication of the Hellenic Society of Gastroenterology,* 26**,** 243-248.

Ko, Y., Butcher, R. & Leong, R. W. 2014. Epidemiological studies of migration and environmental risk factors in the inflammatory bowel diseases. *World Journal of Gastroenterology: WJG,* 20**,** 1238-1247.

Lakatos, P. L. 2006. Recent trends in the epidemiology of inflammatory bowel diseases: up or down? *World J Gastroenterol,* 12**,** 6102-8.

Lakatos, P. L. 2009. Prevalence, predictors, and clinical consequences of medical adherence in IBD: How to improve it? *World Journal of Gastroenterology: WJG,* 15**,** 4234-4239.

Lakatos, P. L., Fischer, S., Lakatos, L., Gal, I. & Papp, J. 2006. The current concept on the pathogenesis of inflammatory bowel disease-crosstalk between genetic and microbial factors: pathogenic bacteria and altered bacterial sensing or changes in mucosal integrity take "toll"? *World J Gastroenterol,* 12**,** 1829-41.

Mahalli, A. A. E. & Alharthi, H. M. A. 2017. Assessment of health-related quality of life of patients with inflammatory bowel diseases in Eastern Province, Saudi Arabia. *J Infect Public Health,* 10**,** 93-101.

Martin, A., Leone, L., Fries, W. & Naccarato, R. 1995. Quality of life in inflammatory bowel disease. *The Italian journal of gastroenterology,* 27**,** 450-454.

Moradkhani, A., Beckman, L. J. & Tabibian, J. H. 2013. Health-related quality of life in inflammatory bowel disease: psychosocial, clinical, socioeconomic, and demographic predictors. *J Crohns Colitis,* 7**,** 467-73.

NG, S. C., Bernstein, C. N., Vatn, M. H., Lakatos, P. L., Loftus, E. V., JR., Tysk, C., O'morain, C., Moum, B. & Colombel, J. F. 2013. Geographical variability and environmental risk factors in inflammatory bowel disease. *Gut,* 62**,** 630-49.

Pallis, I. M. A. 2002. Quality of health care in inflammatory bowel disease and its assessment. *Annals of Gastroenterology,* 15**,** 143-147.

Rocchi, A., Benchimol, E. I., Bernstein, C. N., Bitton, A., Feagan, B., Panaccione, R., Glasgow, K. W., Fernandes, A. & Ghosh, S. 2012. Inflammatory bowel disease: a Canadian burden of illness review. *Can J Gastroenterol,* 26**,** 811-7.

Ross, S. C., Strachan, J., Russell, R. K. & Wilson, S. L. 2011. Psychosocial functioning and health-related quality of life in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr,* 53**,** 480-8.

Saadah, O. I. 2011. Ulcerative colitis in children and adolescents from the Western Region of Saudi Arabia. *Saudi Med J,* 32**,** 943-7.

Shirazi, K. M., Somi, M. H., Bafandeh, Y., Saremi, F., Mylanchy, N., Rezaeifar, P., Abedi Manesh, N. & Mirinezhad, S. K. 2013. Epidemiological and Clinical Characteristics of Inflammatory Bowel Disease in Patients from Northwestern Iran. *Middle East Journal of Digestive Diseases,* 5**,** 86-92.

Ueno, F., Nakayama, Y., Hagiwara, E., Kurimoto, S. & Hibi, T. 2017. Impact of inflammatory bowel disease on Japanese patients' quality of life: results of a patient questionnaire survey. *Journal of Gastroenterology,* 52**,** 555-567.

Vavricka, S. R., Gubler, M., Gantenbein, C., Spoerri, M., Froehlich, F., Seibold, F., Protic, M., Michetti, P., Straumann, A., Fournier, N., Juillerat, P., Biedermann, L., Zeitz, J., Misselwitz, B., Scharl, M., Heinrich, H., Manser, C. N., Safroneeva, E., Raja Ali, R. A., Rogler, G., Schoepfer, A. M. & Greuter, T. 2017. Anti-TNF Treatment for Extraintestinal Manifestations of Inflammatory Bowel Disease in the Swiss IBD Cohort Study. *Inflamm Bowel Dis,* 23**,** 1174-1181.

Vogelaar, L., Spijker, A. V. T. & Van Der Woude, C. J. 2009. The impact of biologics on health-related quality of life in patients with inflammatory bowel disease. *Clinical and experimental gastroenterology,* 2**,** 101-109.

Zhang, Y. Z. & Li, Y. Y. 2014. Inflammatory bowel disease: pathogenesis. *World J Gastroenterol,* 20**,** 91-9.