HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH CROHN'S DISEASE

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SCHOOL OF MEDICINE

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1. INTRODUCTION

1.1. Definition

Inflammatory bowel disease (IBD) is a term which includes two major diseases: ulcerative colitis (UC) and Crohn's disease (CD). These two diseases have overlapping pathologic and clinical features. Moreover, their pathogenesis is not completely understood (1).

UC is a chronic inflammatory intestinal condition distinguished by relapsing and remitting intervals of inflammation restricted to the mucosal layer of the colon. It typically involves the rectum and extends in a continuous way throughout the entire colon. (2,3).

In contrast, CD is a chronic disorder of unresolved etiology which involves the entire gastrointestinal tract from the mouth to the perianal area in a transmural fashion. However, involvement of regions as the mouth, esophagus and proximal small bowel are less frequent. Transmural inflammatory nature of CD may promote more commonly sinus tracts which gives rise to micro perforations and fistulae together with fibrosis and strictures. Sometimes CD may lead to obstruction of the gastrointestinal tract, and this clinical manifestation is more commonly seen in CD than in UC (1,4).

1.2. Epidemiology

The highest annual incidence of CD was greater in North America compared to Europe, Asia and Middle East. Regarding prevalence, Europe and North America showed the highest prevalence values for CD. Additionally, CD was reported as more common in North America than in any other region (5). The incidence and prevalence of CD seems to be lower in Asia and Middle East. However, in Africa, Asia, and South America, the incidence of IBD has been rising (6). In addition, trends in the incidence of CD have been related to gender, age, geographic areas and even to seasons. In a study using data from the Rochester Epidemiology Project, younger age was associated with higher incidence of CD (7).

In Croatia, the incidence of these conditions has been increasing during the last decade (8). The first retrospective study conducted in Split-Dalmatia County with newly diagnosed CD during the nine-year period (2006–2014) showed a six-fold rise of annual incidence of this disease. Furthermore, gender differences were not significant and the onset of CD was most common in the 18–30 age group. Regarding severity, most patients presented with severe form (9).

1.3. Pathophysiology

The etiology of CD is unknown; however, understanding of CD pathogenesis has dramatically increased in the past years. Generally accepted theory supports that this disorder is an immune-related condition affecting genetically susceptible subjects. According to it, the disease starts by environmental factors influencing the mucosal barrier and disrupting the balance between the microbiota of the gut which results in an abnormal gut immune response (10).

Additionally, any disruption of the epithelial barrier could lead to the access of these antigens and their interaction with antigen presenting cells located in the *lamina propia*. These cells are in charge of presenting the antigen to the CD4+ lymphocytes and start releasing cytokines like IL-12 and IL-18 causing differentiation of TH_1 cells. On the other hand, TH_{17} and T regulatory cells are in charge of limiting immune and inflammatory events in the GI tract contributing to its normal balance, thus any alteration that can influence them could relate to the pathogenesis of CD. Furthermore, expansion of regulatory T cell subsets is mediated by TGF-β and IL-6. Also, TH_1 cells release different cytokines as INF-γ and TNF-α which activates macrophages and allows the release of additional molecules.

Moreover, activation of resident immune cells like neutrophils recruits other leukocytes which are able to infiltrate with the help of cell adhesion molecules (integrins). It is worth mentioning that histologically CD shows lesions allocated in a transmural fashion with infiltrated lymphocytes, macrophages, granulomas and fibrosis which might somehow reflect all these cellular and molecular interactions characteristic to CD. Thus, IL-12, IL-17, IL-18, IL-21, IL-22, IL-23, IL-26, INF-γ, TNF-α,TH_1 and TH_{17} cells are the main molecular and cellular elements playing a role in the pathogenesis of this disorder (11,12).

Other known dominant molecular mechanisms strongly implicated in CD pathogenesis are nucleotide-binding oligomerization domain-containing-2 (NOD2) and autophagy. NOD2 is a cytosolic pattern recognition receptor that deals with controlling immunity against bacteria, and it is thought to enhance the immune system by several unknown mechanisms. Actually, from all CD susceptibility genes identified until now, NOD2 shows the strongest association (10). Additionally, a defective autophagic response to bacteria can contribute to CD, and in fact autophagy can cooperate with NOD2 for this purpose (13). Furthermore, unresolved endoplasmic reticulum (ER) stress that affects intestinal epithelial cells (IECs) has also been recognized as an important factor initiating gut inflammation in CD (10).

1.4. Risk factors

1.4.1. Genetics

It has been noted that there are genetically determined factors which contribute to CD. However, more than 85% of patients with CD have no family history of the disease (14,15). Additionally, CD has shown higher concordance rates in monozygotic twins and first-degree relatives of patients with increased risk of developing CD. Nevertheless, having a positive family history of CD still remains the strongest risk factor for developing the disease (16,17).

Interestingly, clinical features of the disease such as location and type show a heritable pattern as well. Additionally, earlier onset of the disease and more serious disease in the offspring of affected parents, also advocate a heritable character of CD. (18-21).

Moreover, there are also different critical signaling pathways that have been associated with CD susceptibility such as intracellular innate immune pathways recognizing microbial products in the cytoplasm, the autophagy pathway, pathways regulating adaptive immunity and pathways regulating epithelial function. Also, extra intestinal manifestations of CD are frequently noted in patients with HLA-A2, HLA-DR1, and DQw5 emphasizing potential associations of the condition with major histocompatibility complex (22,23).

Besides genetic susceptibility factors, a number of genetic syndromes have been associated with CD such as Turner syndrome, Hermansky-Pudlak syndrome and glycogen storage disease type 1b both causing a granulomatous colitis pathologically alike to CD (1).

1.4.2. Life-style related factors

Cigarette smoking may increase the risk of CD as well as it’s recurrence, since nicotine and smoking related products may have different impacts on the mucosal immune response, microvasculature and smooth muscle (24).

Regarding diet, antigens from food could produce an immune response culminating with the sudden appearance of CD. A "Western style diet" (fatty processed food) has also been suggested as a potential risk for this disease. Hypersensitivity to cow’s milk, refined sugar intake, animal fat and polyunsaturated fatty acids are all among the implicated dietary risk factors Conversely, continuous dietary intake of fiber, especially from fruits, and physical activity have been linked to a decreased risk for developing CD (25-27).

1.4.3. Environmental factors

Infections imbalance in the gut microbiome is suggested to play a role in the pathogenesis of CD by the association between particular microorganisms (e.g. *Mycobacterium paratuberculosis*, *Salmonella*, *Campylobacter*), gastroenteritis and CD (1,28). Additionally, medications such as antibiotics, isotretinoin, non-steroidal anti- inflammatory drugs and oral contraceptives have been related to the potential development of CD. Moreover, appendectomy also appears to increase the risk of CD (29-33).

1.5. Clinical presentation

Symptoms such as diarrhea, abdominal pain, fever, weight loss with or without bleeding are common in CD. Crampy abdominal pain is frequent and could be attributed to fibrotic stricture formation during the inflammatory process which could even lead to intestinal obstruction. If the disease is limited to the ileum, a patient commonly presents with right lower quadrant pain similar to that experienced in appendicitis. Actually, a common clinical presentation frequently is a young patient complaining of right lower quadrant abdominal pain, weight loss and diarrhea (1,34). An inflammatory mass may be also palpated in that region.

Additionally, patients' history of chronic diarrhea without any bleeding but together with other typical manifestations of CD (e.g., arthralgia, eye or skin problems) highly suggests the diagnosis of this condition.

Moreover, transmural nature of CD confers the ability to develop sinus tracts leading to fistulas (e.g. enterovesical, enterocutaneous, enteroenteric, enterovaginal) and obviously their clinical manifestations depend on the area affected by this process (28).

Additionally, more than one-third of patients suffer from perianal disease consequences like anal fissures, anorectal fistulas and perirectal abscesses which may even dominate the whole clinical picture (35). Involvement of the distal ileum leads to malabsorption with the subsequent watery diarrhea and steatorrhea that could produce serious malnutrition problems, clotting issues, hypocalcemia and hypomagnesemia among others (1).

Involvement of other parts of the gastrointestinal tract is very variable and infrequent and can give rise to oral manifestations such as aphthous ulcers, esophageal symptoms like odynophagia or dysphagia and gallstones. With gastroduodenal involvement epigastric pain, nausea and vomiting can also occur (36). Additionally, weight loss can be related to

malabsorption but also to reduced food intake since patients feel better when they do not eat if they are undergoing an obstructive intestinal process (1).

1.5.1. Extra intestinal manifestations

Extra intestinal manifestations are more frequent when colon is affected by CD. Arthritis which is the most common extra intestinal manifestation mainly involves large joints (37). Axial or central arthritis like sacroileitis or ankylosing spondylitis may appear as well and can even be the first manifestation of the disease.

Eye symptoms include episcleritis, uveitis and iritis. Erythema nodosum is the most relevant skin disorder related to CD. Moreover, primary sclerosing cholangitis is another extra intestinal manifestation that can present in correlation with the degree of disease activity (38,39).

Additionally, secondary amyloidosis which is quite rare can produce renal failure and involve other systems (40). Venous and arterial thromboembolism due to hypercoagulability can also occur (41,42). Calcium oxalate and uric acid renal stones may also be present in CD accompanied by steatorrhea and diarrhea (43). Megaloblastic anemia due to vitamin B12 deficiency in serious ileal involvement can also occur (44).

1.6. Complications

Severe perianal disease, toxic megacolon, perforation, obstruction, massive hemorrhage, malabsorption, intraabdominal and pelvic abscesses are known complications of CD (1). Additionally, patients with this condition have an increased risk for developing colorectal cancer when they become affected by colitis or an increased risk for small bowel carcinoma when they suffer from enteritis together with colonic involvement. Therefore, cancer can also be considered a long-term complication of this disease (4).

Moreover, CD patients have an increased risk for venous thromboembolism and pulmonary embolism, and prophylaxis with low molecular weight heparin is recommended in hospitalized patients (45,46).

1.7. Diagnosis

The diagnosis of CD is made on the basis of clinical history, endoscopic and histologic findings together with imaging studies because physical examination may be normal or nonspecific (34). Additionally, there is no specific diagnostic test to confirm the disease (4).

Laboratory studies include complete blood count, blood chemistry (blood glucose, electrolytes, liver enzymes, renal function tests), C-reactive protein, erythrocyte sedimentation rate, serum vitamin B12 levels, iron and vitamin D (47).

Common laboratory findings are thrombocytosis, anemia, hypoalbuminemia, vitamin deficiencies and increased acute phase reactants (particularly C-reactive protein) (34). Levels of C-reactive protein are noted to correlate with the activity of the disease (48).

Endoscopy is considered the gold standard for diagnosis. When performing colonoscopy, endoscopic characteristics include focal ulcerations next to areas of normal mucosa together with polypoid mucosal changes that confer a "cobblestone" appearance (34).

Rectal sparing is also frequent but biopsies should be always obtained from rectum, right colon and left colon even if the mucosa looks normal in order to look for microscopic inflammation. The major findings on the intestinal biopsy include focal ulcerations together with acute and chronic inflammation which are confirmatory instead of diagnostic. Granulomas are also seen and become diagnostic when infections, lymphoma or rheumatic conditions such as Bechet's disease are ruled out (49).

In the case of small bowel involvement, wireless capsule endoscopy is an option to visualize this region. Imaging studies serve to assess the upper gastrointestinal tract and information about strictures can be obtained from areas colonoscopy cannot cover (34).

Furthermore, other methods to diagnose CD include conventional upper gastrointestinal series with CT and CTE, MRI and MRE, ultrasound and enteroclysis. Characteristic features observed with the use of upper gastrointestinal series include a narrow lumen which represents "string sign", ulceration and nodularity, fistulas and abscesses, a "cobblestone" appearance and bowel loops separation due to bowel wall thickening in case of transmural inflammation. CT and CTE are also useful in the evaluation of complications, the latter one being considered as the main procedure for small bowel in case of concern regarding abscess formation. Ultrasound can also be used for small bowel imaging and the most relevant finding is considered to be an increase in the bowel wall thickness more than 3 mm (37).

Options for the perianal area include magnetic resonance imaging for perianal fistula detection and endoscopic ultrasound for those patients who are not suitable for the aforementioned technique. Endoscopic ultrasound sometimes may even avoid the need for

surgical exploration. In addition, magnetic resonance imaging can also be useful when monitoring response to therapy in CD (4).

Interestingly, multispectral optoacoustic tomography is a technique that is not yet available but it is promising for assessment of the disease activity (active versus non active disease) detecting bowel wall inflammation by hemoglobin-dependent tissue perfusion among other markers (50).

Furthermore, Antibody testing for pANCA and ASCA may help differentiating between UC and CD, ASCA being more related to CD. These tests should never be used for screening but as an adjunct to clinical picture and typical testing modalities (49).

When distinguishing between CD and functional bowel inflammation, stool markers such as calprotectin or lactoferrin can be used before undergoing ileocolonoscopy. If these markers are normal CD is improbable, if the results are high ileocolonoscopy and biopsy are advised in order to confirm the diagnosis of the disease. Fecal calprotectin can also be used to monitor patients with clinical remission but presenting with unexpected flares (34). Additionally, in the case of suffering from diarrhea, a stool specimen must be sent for culture and investigation looking for *C. difficile* toxin ova and parasites among others (49).

1.8. Differential diagnosis

Irritable bowel syndrome, ulcerative colitis, infectious colitis, ischemic colitis, diverticular colitis, lactose intolerance, carcinoma, tuberculosis and lymphoma must be considered in the differential diagnosis of CD. When acute diarrhea is present infection must be ruled out. *Shigella, Salmonella*, *Campylobacter, Yersinia*, parasites, *Clostridium difficile* and *Escherichia coli* 0157:H are all potential microorganisms that can cause diarrhea mimicking CD. In case of immunocompromised patients, cytomegalovirus infection can simulate this condition. *Yersinia* may also cause acute ileitis difficult to distinguish clinically from CD ileitis (1,28).

Additionally, it is always essential to differentiate between UC and CD, especially when CD involves the colon since medical and surgical management are completely different for each of them. When distinction cannot be made between these two entities, the condition is referred to be an indeterminate colitis and sometimes the diagnosis can even evolve from one condition to the other (1,28)

1.9. Prognosis

The course of this condition is typically characterized by intermittent exacerbations followed by periods of remissions (1,28). Factors associated with a more severe and complicated course include initial need for glucocorticoids, age younger than 40 years, smoking, perianal or rectal disease and low educational level (51,52). Around 80% of patients suffering from CD need hospitalization during the course of the disease and for most patients symptoms are chronic and intermittent what is more common than continuous disease activity or prolonged remission (53). Surgical intervention is required in many cases especially due to worsening of the symptoms, lack of response to medical treatment and complications such as obstruction or perforation (54).

Regarding mortality outcomes and the possibility that CD can decrease life-expectancy, heterogeneity of the disease makes it difficult to draw an accurate conclusion but some studies have shown that life expectancy might be slightly reduced (55).

1.10. Assessing disease activity

Clinically, disease activity can be classified as mild to moderate or as moderate to severe. If the patient is capable to tolerate oral nutrition and if symptoms like toxicity, painful mass, dehydration, obstruction, abdominal tenderness, and more than 10% weigh loss are absent, disease is referred to as mild to moderate. Moderate to severe disease includes more prominent symptoms of fever, abdominal pain, weight loss, nausea and vomiting without obstruction or anemia and lack of response to previous treatment. Lastly, severe to fulminant disease must be considered when symptoms persist despite glucocorticoids use, and intractable vomiting, high fevers, rebound tenderness, intestinal obstruction or presence of an abscess occur (28).

Additionally, two frequently used scoring systems used in clinical trials are the Crohn's Disease Activity Index (CDAI) and the Harvey-Bradshaw Index (HBI). This can be translated to clinical practice and identify clinical remission (CDAI <150 corresponding to asymptomatic patient), mild CD disease (CDAI 150-220 corresponding to ambulatory patient who tolerates an oral diet with <10% weight loss and lack of systemic symptoms) and severe or fulminant CD (CDAI >450 corresponding to persistent symptoms even while using glucocorticoids or biologic agents as outpatients or subjects with high fever, intestinal obstruction, continuous vomiting, cachexia, peritoneal irritation or an abscess) (53).

Characteristics of low-risk patients include absence of or mild symptoms, diagnosis at age older than 30 years, normal or slightly increased C-reactive protein or fecal calprotectin levels, limited distribution of bowel inflammation, no prior intestinal surgery, superficial or lack of ulceration on colonoscopy, absence of perianal complications and lack of penetrating or structuring disease (56). Low-risk patients may be reclassified to higher risk in case they suffer from complications or lack answer to treatment. Additional prognostic factors which can suggest that the disease is worsening are presence of extra intestinal manifestations, increased number of flares, hospitalizations, glucocorticoids requirement, and radiologically observed bowel damage (49).

1.11. Treatment

1.11.1. Medical treatment

Medical treatment is the mainstay to treat CD. Step-up therapy and top-down therapy are two common approaches to address the treatment of this condition. While step-up therapy advocates for starting treatment with less potent medications with fewer adverse effects, top down therapy supports the initiation of CD treatment with more potent medications such as immunomodulatory and/or biologic treatments. Step-up therapy is generally recommended for low-risk patients and more potent medications are given when disease does not respond to the initial treatment or when patients require more than a course of glucocorticoids. For high-risk patients top-down therapy is suggested, however price of therapy, patient compliance, patient preferences, individual susceptibility to a drug and potential toxicity should also be taken into account in order to make patient-specific decisions. The goal of the treatment for CD is to accomplish histologic, endoscopic and clinical remission by the evidence of mucosal healing. Medications used in the treatment of CD includes mostly glucocorticoids, 5-aminosalicylates, immunomodulators and anti-TNF agents (49).

For low-risk patients with mild CD, the following medications are suggested:

- Glucocorticoids

Budesonide (9 mg by mouth per day, no longer than 12 weeks) is recommended for inducing remission when ileum and proximal colon are involved. It has fewer adverse effects than conventional glucocorticoids such as prednisone which is also an alternative for patients who do not respond to budesonide. The initial dose of prednisone is 40 mg per day for one week. Conventional glucocorticoids are recommended as first-line therapy for inducing remission but should never be used as maintenance therapy due to their adverse-effect profile. These

medications should be gradually tapered and discontinued once remission is achieved or recommended treatment duration has been attained. When there is clinical recurrence after achieving remission following glucocorticoid therapy, a second course of glucocorticoids can be started and even a thiopurine and/or a biologic agent can be added (3,12).

- 5-aminosalicylates

Its use is indicated for limited ileocolonic involvement, especially for those patients who want to avoid glucocorticoids. For limited ileitis an agent as mesalamine is indicated and even preferred instead of sulfasalazine due to its adverse-effect profile (e.g. nausea, fever, pancreatitis, rash, pneumonitis, and headache). Additionally, sulfasalazine is less useful for ileitis, therefore it is reserved just for treatment of colitis (12). It is also worth mentioning that it is still not clear whether budesonide is more effective to induce remission compared to mesalamine (3,12).

After discontinuation of glucocorticoids or 5-aminosalicylates, clinical observation and follow-up with ileocolonoscopy is advised in six to twelve months. Other therapies for mild CD include antidiarrheal medications as a symptomatic treatment for those patients who do not respond entirely to first-line therapy. Some options include loperamide in small doses (2 to 4 mg after a diarrheic episode), cholestyramine for non-stricturing CD and colestipol or colesevelam for those patients who are not able to tolerate the aforementioned medications (12).

Dietary interventions may also be considered since patients with ileal CD have an increased tendency for lactose intolerance and lactose avoidance may definitely be beneficial in this context. Other dietary interventions like multivitamins and elimination diets cam also be helpful. Additionally, bowel rest and total parenteral nutrition are as efficient as glucocorticoids at inducing remission of active disease but not for maintenance therapy (1,49).

For high-risk patients with moderate to severe CD, glucocorticoids are frequently suggested as first initial medical therapy especially for patients who require a fast response. Thus, a course of glucocorticoids should be used in the short-term and may serve as a bridge to a maintenance therapy. Prednisone initiated at a dose of 40 mg orally up to four to eight weeks is preferred but budesonide can be used as an alternative specially when there is ileal involvement. If the patient is hospitalized with an exacerbation of the disease, intravenous glucocorticoids are recommended. Those patients who are suffering from a complication should be assessed by fluid and electrolytes replacement, intravenous antibiotics, consultation

with a gastrointestinal surgeon and nutritional assessment since parenteral nutrition may be needed (1,49).

Another possibility to induce and maintain remission is top-down approach with combination therapy using a biologic agent such us tumor necrosis factor-alpha inhibitor in combination with an immunomodulators like azathioprine, 6-mercaptopurine, or methotrexate (57). With this combination a synergistic effect is obtained and disease can be managed targeting different mechanisms involved in its pathogenesis. This combination also reduces immunogenicity against biologic agents which happens frequently when the therapy is started. In addition, combination therapy also enhances the pharmacokinetics of the biologic treatment (47).

Moreover, anti-tumor necrosis factor-alpha in combination with a thiopurine is more effective for induction of remission when compared to thiopurine and anti-tumor necrosis factor-alpha (infliximab) separately (58).

Anti-tumor necrosis factor-alpha agents used for CD include: infliximab, adalimumab and certolizumab pegol. The first two are preferred for induction of remission and all three can be used for maintenance. Certolizumab pegol can be used as a second- or third-line therapy in patients who became intolerant to the other two agents (58).

An alternative to combination therapy are anti-tumor necrosis factor-alpha as monotherapy especially indicated for patients with contraindication to thiopurines like prior adverse reaction or an abnormal TPMT enzyme. Furthermore, for patients older than 60 years, young male patients, patients with history of Epstein Barr virus, patients with high risk for malignancy or serious infections and those who prefer to avoid immunomodulators, monotherapy remains a possible option (58).

Moreover, in cases of moderate to severe CD, when the patient becomes glucocorticoid-dependent immunomodulators such as azathioprine, 6-mercaptopurine or methotrexate can be used (47).

Natalizumab is a monoclonal antibody against alpha-4 integrin effective for the induction of remission especially in those who cannot tolerate anti-tumor necrosis factor-alpha, however it is associated with serious adverse effects like progressive multifocal leukoencephalopathy and it is mostly reserved for patients suffering from CD together with multiple sclerosis. The use of this agent is not recommended in patients with impaired immunity or taking tumor necrosis factor-alpha inhibitors, additionally glucocorticoids and

immunomodulators should be stop months before using natalizumab. Neutrophil and leukocyte counts should be also taken into consideration before initiating this treatment (59).

Maintenance therapy for high-risk moderate to severe disease may include anti-tumor necrosis factor-alpha monotherapy or combination therapy. The duration of this treatment is unclear but many patients will demand lifelong therapy with at least one of these agents. Additionally, methotrexate constitutes an alternative for patients who cannot tolerate thiopurines (47).

For perianal disease, metronidazole and ciprofloxacin are frequent antibiotics used for perianal fistulas. They produce symptomatic improvement and diminish drainage. Other additional agents that are still being used for this condition are thiopurines especially if there is no remission after antibiotic treatment. Lastly, surgical treatment may be necessary in serious cases unresponsive to medical treatment (35).

1.11.2. Surgical treatment

Surgical treatment is not curative and recurrence after operative management is the rule for CD thus, surgical indications are mostly limited to the complications of the disease, to the lack of response to medical treatment and to the presence of growth delay in children suffering from this condition (60).

Common surgical procedures include small bowel resection, strictureplasty and endoscopic balloon dilation. Small bowel resection can be performed either laparoscopically or with an open approach but the first one is preferred (47). This procedure is actually the most effective for patients with short-segment structuring or fistulizing disease in order to restore health and improve quality of life (61,62).

Additionally, surgical procedures frequently used to treat CD in the presence of colitis or proctitis include: segmental colectomy, total colectomy with ileorectal anastomosis, total proctocolectomy with end ileostomy and proctectomy (47). Strictureplasty is convenient for those patients who have lost considerable length of small bowel due to previous surgeries and constitutes an alternative to bowel resection (60).

Endoscopic balloon dilation can be performed in a subset of patients who wish to avoid surgery and it is only effective for short strictures less than five centimeters (63). Moreover most patients end up developing recurrences and requiring additional surgery (47).

1.12. Quality of life

Previous studies conducted among patients with CD have observed a decrease in patients' quality of life. Furthermore, higher rates of depression and anxiety were noted (64). Additionally, a recent systematic review stated that quality of life in patients with CD is poorer compared to healthy subjects and especially poor for those patient with active disease compared to those with dormant disease. When concerning quality of life, mental functioning is peculiarly affected (65,66). Health-related quality of life (HRQOL) means a state of well-being that is composed of the capability to perform every day activities while experiencing physical, psychological and social well-being together with patient satisfaction with its own functionality. Quality of life in CD is not only related to symptoms, there are many other important factors that frequently go unnoticed and should be taken into consideration such us disease chronicity, recurrences, extra intestinal manifestations, adverse effects of medical and surgical treatment, surgical stress together with its psychological impact and fear of developing cancer among others. All these factors have a daily impact on quality of life leading to a consequent reduction on HRQOL.

Additionally, patients with severe disease, patients with inadequate sleep quality and lack of folic acid intake show lower HRQOL scores. Folic acid deficiency can be frequent in these patients due to the chronic inflammatory nature of the disease, malabsorption and the adverse effects of long-term therapy (67).

Many other factors such as disease activity, number of flare-ups and hospital admissions influence HRQOL (68). However, one of the most relevant factors in CD seems to be flare-ups which can have qualitative and quantitative impact (69,70). Given these facts, measurement of HRQOL is important in the evaluation, management and follow-up of patients with CD. The most frequently used instrument to measure HRQOL is the 32-item version of Inflammatory Bowel Disease Questionnaire (IBDQ-32). It has been noted that perception of greater quality of life is an indispensable factor tremendously beneficial in the treatment of chronic conditions. Effects of organic symptoms together with other dimensions including social, financial, psychological, spiritual and functional are the main field of HRQOL.

Indeed, an evaluation of influence of health on those dimensions is performed using specific questionnaires. IBDQ-32 questionnaire consists of 32 items in 4 main domains which include gastrointestinal symptoms, systemic symptoms, emotional involvement, and social impact. Responses to each of the items are scored on a scale consisting of 7 points where 7 is

considered the best and 1 is considered the poorest perceived HRQOL (68). The total IBDQ score is the sum of the answers to each of the individual IBDQ questions. Overall IBDQ score can vary from 32 (very low HRQOL) to 224 (excellent HRQOL) (71). The IBDQ-32 has been translated and verified in approximately 93 languages and this tool is definitely the most popular measure with vigorous evidence of being accurate and consistent enough for adults suffering from CD (72). IMPACT-III (HR) is another example of specific questionnaire to measure HRQOL in the pediatric population with CD, and its five domain structure which is based on 33 items seems to be the most appropriate tool for measuring HRQOL in Croatian children with CD (73).

World Health Organization defines CD as a disease that can influence psychological, physical, social and familial aspects of life. Psychological and physical involvement may present as emotional or physical distress, lack of independence and sexual function impairment among others (68). CD patients often present diminished levels of sexual satisfaction in comparison with the general population (74). Additionally, a quarter of woman with CD totally evade sexual interaction mainly due to symptoms like abdominal discomfort, diarrhea and potential fecal incontinence. Furthermore, depression seems to be the major cause of impairment in sexual activity in both genders (67,75).

Hence, HRQOL is important for the assessment of the impact of the disease and also allows evaluation of CD therapy since therapy substantially affects quality of life (67). As an illustration, when iron is given for anemia in CD, an improvement in quality of life can be observed (67).

Similarly, quality of life is also improved in patients receiving iron with or without erythropoietin when they present with anemia accompanied with chronic renal failure (75).

2. OBJECTIVES

OBJECTIVES:

The aim of this study was to determine health-related quality of life in patients with Crohn's disease.

HYPOTHESIS:

1. Patients with Crohn's disease will report low quality of life.
2. Patients with active disease will have lower quality of life when compared to patients with inactive disease.

3. SUBJECTS AND METHODS

3.1. Study design

A questionnaire-based cross-sectional study was conducted at the University Hospital of Split (Department of Gastroenterology and Hepatology) and at the University of Split School of Medicine (Department of Pathophysiology). The study was conducted during six months period performed (December 2017-May 2018).

3.2. Ethical considerations

All participants included in the study provided informed consent. The study protocol was approved by both the Ethics Committee of the University Hospital of Split and the Ethics Committee of the University of Split School of Medicine. All procedures performed in studies were in accordance with the ethical standards of the 1964 Helsinki declaration and institutional and national research committee.

3.3. Subjects

This study included 30 patients diagnosed with Crohn's disease. The diagnosis was based on the history, as well as clinical, radiological, endoscopic and histological features in accordance with European Crohn's and Colitis Organisation (ECCO) evidence-based consensus on the diagnosis and management of Crohn's disease (37,76). Remission is defined as complete absence of symptoms self-reported from the patient. Information about disease duration was obtained from patients' medical documentation.

A medical history interview was conducted with all the patients included in the study. Physical examination was performed and anthropometric measurements were taken. Measurements of body height and weight were taken and body mass index (BMI) was calculated.

3.4. HRQOL assessment

Health-related quality of life (HRQOL) was measured with Inflammatory Bowel Disease Questionnaire which has been well established instrument for IBD specific HRQOL assessment. Inflammatory Bowel Disease Questionnaire is a 32-item health survey that includes 10 bowel symptoms related questions, 5 systemic symptoms related questions, 12 emotional function related questions and 5 questions relating to social function.

The response to each question is structured upon a seven-point scale in which 7 represents the best, and 1 represents the worst function. This translates to a maximum score of 70 for bowel symptoms, 35 for systemic symptoms, 84 for emotional function and 35 for the social function domain (77).

3.5. Statistical analysis

Statistical analysis of the data was performed using software MedCalc ver. 11.5.1.0 for Windows (MedCalc Software, Ostend, Belgium). Data presented as mean±standard deviation for quantitative variables and as whole numbers (proportion) for qualitative variables. Normality of the data distribution was assessed using Kolmogorov-Smirnov test. Mann-Whitney U test was used for comparison of different domains of IBDQ-32 between patients with reference to the activity of their disease. Pearson's correlation coefficient was used for assessment of correlation between IBDQ-32 and disease duration or self-perceived quality of life. The statistical significance was set at $P<0.05$.

4. RESULTS

Table 1 shows the demographic and anthropometric features of the 30 patients. Male patients predominated and more than half of overall patients had active disease. The present study included patients with various disease durations (range 0.5-47.0 years).

Table 1. Patients' characteristics

Variable	Crohn's disease patients (N=30)
Age (years)	37.9±14.3
Gender	
Men (N)	20 (66.7%)
Women (N)	10 (33.3%)
Weight (kg)	73.79±17.5
Height (cm)	177.48±9.86
BMI (kg/m^2)	22.41±5.90
Disease duration (years)	9.95±9.64
Disease active (N)	20 (66.7%)

Data are presented as mean±standard deviation or as number (percentage) where appropriate
BMI – body mass index

Table 2 shows the overall score and the scores from all the different domains explored in patients with active and not active disease. There were no statistically significant differences observed between overall score among patients with active compared to patients with not active CD and the same applies for all the domains.

Table 2. IBDQ-32 domains relative to disease activity

	Disease active (N=20)	Disease not active (N=10)	*P**
Overall score	162.5 (139.0-194.5)	189.5 (169.0-196.0)	0.159
Gastrointestinal symptoms domain	55.0 (42.0-59.5)	58.5 (55.0-63.0)	0.153
Systemic symptoms domain	25.5 (19.5-28.5)	26.5 (22.0-30.0)	0.495
Social impact domain	26.0 (22.0-32.5)	32.0 (31.0-33.0)	0.081
Emotional involvement domain	58.5 (48.5-71.5)	70.5 (58.0-73.0)	0.218

Data are presented as median (interquartile range)
*Mann-Whitney U test

The correlation between disease duration and IBDQ-32 domains are presented in Table 3, showing no significant correlations between disease duration and any of the studied IBDQ domains.

Table 3. Correlation between disease duration and IBDQ-32 domains

	r	*P**
Overall score	-0.176	0.353
Gastrointestinal symptoms domain	-0.140	0.462
Systemic symptoms domain	-0.217	0.249
Social impact domain	-0.173	0.360
Emotional involvement domain	-0.138	0.466

*Pearson's correlation

Figure 1 shows that perception of quality of life for these patients was positively correlated with overall score (r=0.506; P=0.004).

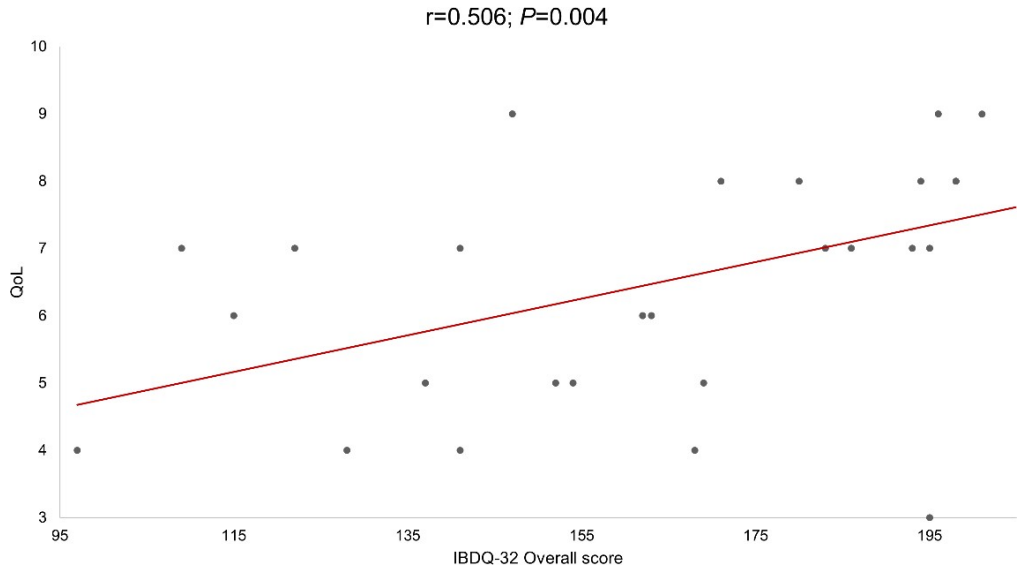

Figure 1. Correlation between quality of life and IBDQ-32 Overall score

Interestingly, perception of quality of life was not related to gastrointestinal symptoms as shown in figure 2. Positive correlation was found but it was not statistically significant.

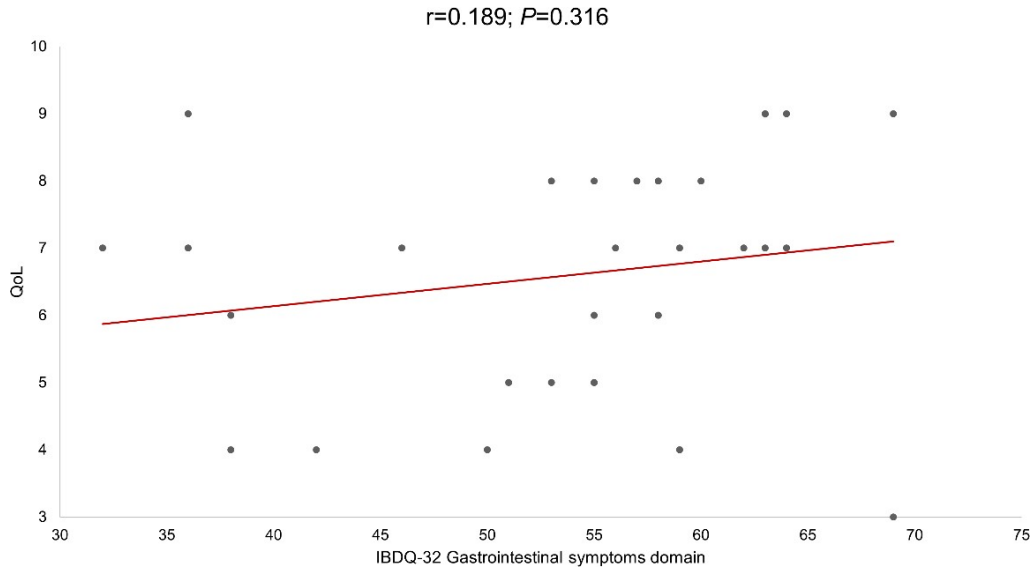

Figure 2. Correlation between quality of life and IBDQ-32 Gastrointestinal symptoms domain

Systemic symptoms (r=0.629; P<0.001), emotional involvement (r=0.588; P<0.001), together with social impact (r=0.458; P<0.011), domains were all positively correlated with self-perception quality of life as shown in figures 3, 4 and 5.

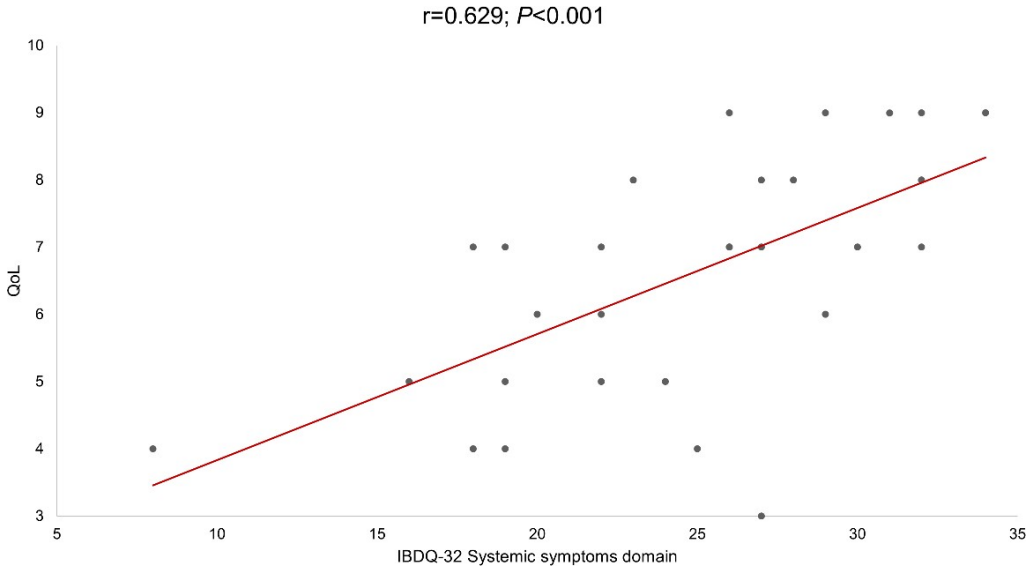

Figure 3. Correlation between quality of life and IBDQ-32 Systemic symptoms domain

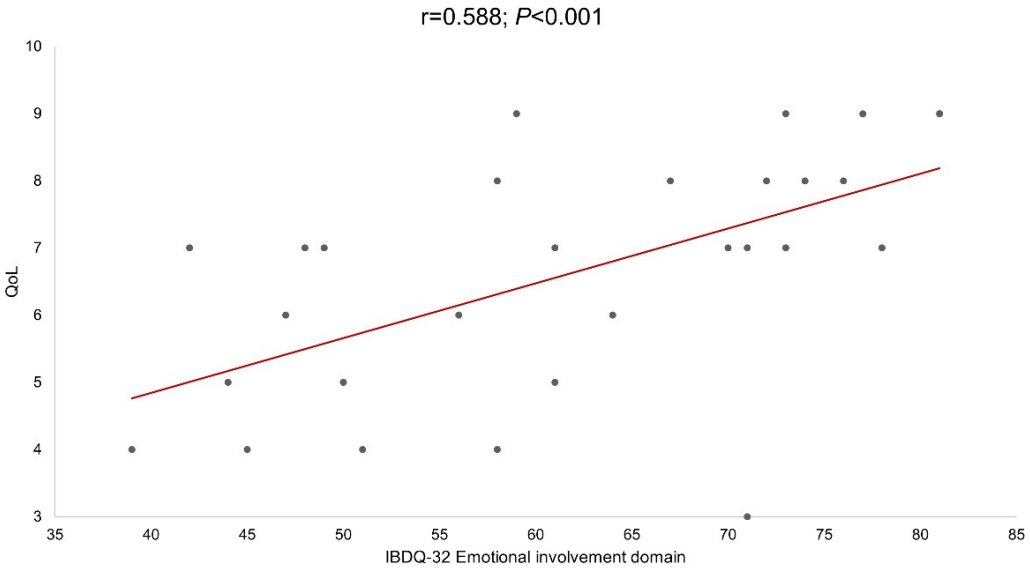

Figure 4. Correlation between quality of life and IBDQ-32 Emotional involvement domain

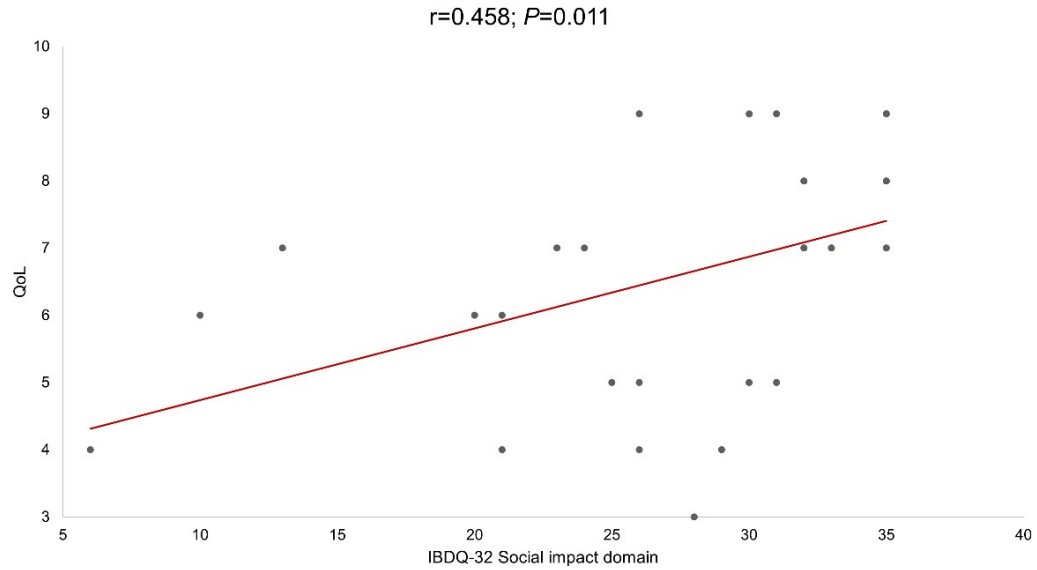

Figure 5. Correlation between quality of life and IBDQ-32 Social impact domain

Figure 6 reflects the averaged mean overall score and the mean scores for the different domain obtained from the IBDQ-32 questionnaire. Interestingly, the social impact domain shows the higher score translated into better perceived quality of life in this setting. Conversely, systemic symptoms domain is the domain which seems most affected with the lowest score and thus lowest perceived quality of life related to this domain.

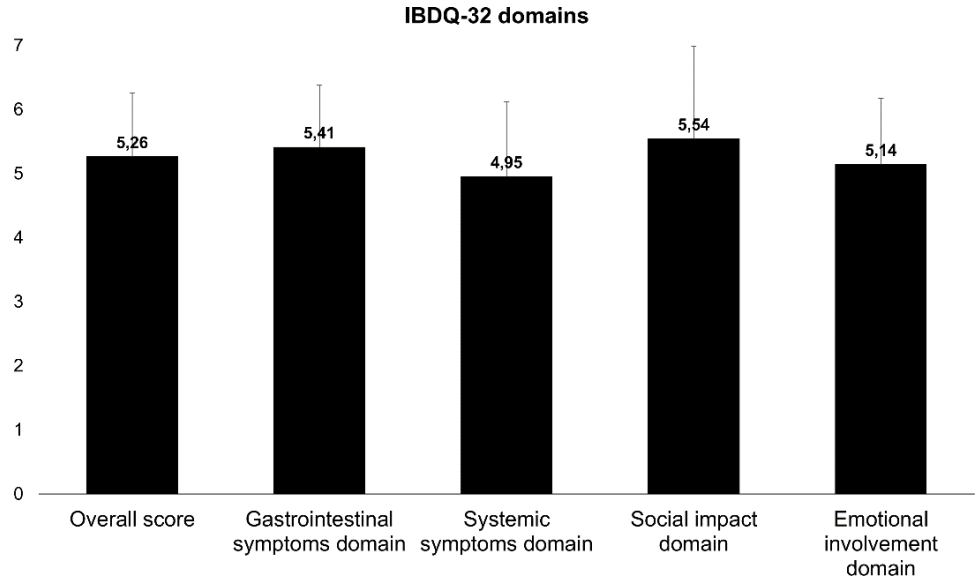

Figure 6. Mean score for the different domains of IBDQ-32

5. DISCUSSION

CD profoundly affects well-being of patients with a substantial negative impact and impairment in HRQOL as it has been observed in many previous studies (64,78). During the past years, studies investigating quality of life in CD have dramatically increased with currently a total of more than 400 publications each year since 2013. This fact emphasizes the relevance of HRQOL in this condition (66).

IBDQ-32 questionnaire has been shown to be a valid and sensitive instrument which can be used to assess HRQOL in CD patients even in countries with different languages, culture and life-style (79,80). Additionally, if applied at the beginning and during pharmacological treatment, it can be used to assess the clinical course of the disease, and its relation to quality of life.

This questionnaire also provides excellent psychometric properties in terms of credibility, reproducibility and sensitivity to changes (81).

We have found heterogeneous results compared to other studies since some of our findings can relate to previous published data, while others show a different pattern. For instance, in this study no correlation was found with bowel symptoms and HRQOL in contrast to the other studies where a significant correlation was noted (82).

Additionally, no difference was observed in this study between active and not active disease in any of the domains in contrast to previous studies where one of the main findings was the correlation between disease activity and HRQOL (82-86).

On the other hand, no statistically significant correlation was demonstrated between disease duration and IBDQ scores and the same finding was also noted in other studies (82). However, there is controversial data since other authors support that patients with longer disease duration have a better HRQOL probably due to a disease adaptation process or due to treatment engagement (87-89).

The authors of IBDQ-32 questionnaire, established that a low quality of life corresponds to an overall score between 32 and 95, moderate includes a range between 96 and 159 and high quality of life is considered to correspond to an overall score between 160 and 224 points (77). Therefore, patients in this study are considered to have high quality of life according to the aforementioned classification since the overall score for these patients was

162.5 for active disease and 189.5 for inactive disease. Additionally, in the present study, the higher score on the IBDQ-32 questionnaire was for the social domain which is translated into a better quality of life in this setting for these patients, compared to the systemic symptoms domain which showed the lowest score and consequently the lowest quality of life. Conversely, other studies showed a different pattern regarding domains scores and in one of the studies social domain had the lowest score (82). In other studies, systemic symptoms domain showed the lowest score in contrast to this study where it showed the highest. Thus, given the above it can be concluded that IBDQ domains score distribution also changes between studies and countries reflecting the versatility of this condition in relation to external factors.

In this case, the higher score on the IBDQ-32 questionnaire was for the social domain which is translated into a better quality of life in this setting for these patients, compared to the systemic symptoms domain which showed the lowest score and consequently the greatest impact of the disease on this domain.

Considering that the systemic symptoms domain was the one with lowest score in the subset of patients observed in this study, use of effective treatment regimens aiming to reduce sleep disorders, fatigue and all other complains belonging to this domain is of great importance and should be encouraged for these patients. Thus, effective treatment for CD patients seems to play a key role on improvement of HRQOL.

The most important findings of this study are presented in figures 1-5 where self-perception of quality of life was positively correlated to overall score, systemic symptoms, emotional involvement and social impact domain. These robust findings are important since CD is associated with a substantial psychosocial burden with social and interpersonal function impairment. Its course can be chronic, unpredictable characterized by embarrassing symptoms and patients might live worried about several aspects like social isolation, bowel control or fear of developing cancer among others (90).

Additionally, previous studies observed that rates of anxiety and depression were higher in patients with CD than in healthy population (64). Thus, psychological conditions and how

the patient sees this under their subjective evaluation are also relevant factors of quality of life (32).

Regarding work-life and employability, it can also be negatively affected by this disease with the consequent absenteeism, reduced work ours and financial impact (91-93).

It should also be noted that HRQOL is not a well-recognized indicator of disability and CD is not considered a disabling disease compared to other more severe chronic inflammatory conditions such as multiple sclerosis (94). Additional research is needed to measure disability in CD patients. However, social domain which includes ability to participate in social activities and to work showed the highest score in this study and was then associated with a better quality of life. Nonetheless, previous studies have demonstrated that HRQOL is significantly impaired by work disability and ability to work of patients with this condition is commonly compromised (95,96).

The systemic symptoms domain was the one with lowest score in the subset of patients observed in this study. Fatigue is a symptom that is included in systemic domain and is commonly experienced by CD patients (97,98). Additionally, fatigue may also substantially impair patient's daily life and is also associated with a decreased HRQOL (97). Thus, the use of effective treatment regimens aiming to reduce fatigue, sleep disorders and all other complains belonging to this domain is of great importance and should be encouraged for these patients.

Additionally, the true impact of this disease is not always readily apparent what leads to a lack of understanding regarding presence and severity of this condition (99). Therefore, effective treatment of patients with CD and management of reversible associated symptoms seems to play a key role on the improvement of HRQOL avoiding unnecessary patient's suffering and distress.

Overall score of the IBDQ-32 questionnaire in this study was 162.5 for patients with active disease and 189.5 for patients with not active disease. Even though these differences were not statistically significant, the fact that previous studies also showed similar results for overall score when using this questionnaire corroborates that this tool is reliable and sensitive (32,71).

Regarding sample size, 30 patients were included in our study what is similar to sample size used in other studies with shared findings (82). Thus, the small population size in this case could be considered a limitation in this study as the fact that 33.3% of patients did not have active disease at the time when the questionnaire was performed. It would be convenient to extent sample size to verify some of the findings.

In the first retrospective epidemiological study of IBD among adult population of Split-Dalmatia County, a significant incident rate increase for the disease was noted. From 130 CD patients male gender predominated what corresponds to the same finding also noted in this study performed in the same region. In the aforementioned study, the onset of CD was most frequent in the 18-30 age group. This fact also corresponds to the approximate age of the patients from the present study. Additionally, 76% of patients presented with severe form, 5% with moderate and 19% with mild form manifesting the potential tendency of patients from this region to suffer from active disease since in the present study more than half of the patients included also had active disease (9).

Lastly, additional research is needed to conclude and stablish the impact of new factors apart from those already being studied in HRQOL. Homogeneity should be reached among studies and discrepancies should be eradicated in order to identify subset of patients and factors that are more likely to correlate either positively or negatively with quality of life. Health services should make sure that the management of patients with CD does not only include symptomatic control and healing, but also the normalization of their quality of life. Therefore, knowledge of the predictive factors and their influence can be used in the design and implementation of health and therapy interventions for the most vulnerable patients in terms of risk of loss of HRQOL.

6. CONCLUSIONS

1. No statistically significant differences in patients with active and not active disease related to quality of life were observed.
2. Self-perception of quality of life was positively correlated to overall score and systemic symptoms, emotional involvement and social impact domain.
3. Perception of quality of life was not correlated to gastrointestinal symptoms.
4. Social impact had the highest score on the IBDQ-32 questionnaire while Systemic symptoms domain had the lowest score on the IBDQ-32 questionnaire.

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8. SUMMARY

Objectives: Quality of life is substantially impaired in patients with CD by being a chronic, remitting and unpredictable entity adversely affecting day to day functioning. The aim of this study was to determine health-related quality of life in patients with Crohn's disease.

Subjects and methods: A total of 30 patients diagnosed with CD performed the Inflammatory Bowel Disease Questionnaire (IBDQ-32) questionnaire consisting of 32 items in order to assess their quality of life and specific patterns potentially characteristic for Split-Dalmatia County.

Results: No statistically significant differences were found in patients with active and not active disease related to quality of life. Perception of quality of life for these patients was positively correlated with overall score ($r=0.506$; $P=0.004$) and interestingly, t a positive correlation was found between their quality of life and gastrointestinal symptoms but it was not statistically significant. Systemic symptoms ($r=0.629$; $P<0.001$), emotional involvement ($r=0.588$; $P<0.001$), together with social impact ($r=0.458$; $P<0.011$) domains were all positively correlated with self-perception quality of life. Additionally, no significant correlations between disease duration and any of the studied IBDQ domains was found. The overall score was 162.5 and 189.5 for active and not active disease respectively. The highest score was observed in social domain while the lowest score was observed in systemic symptoms domain.

Conclusion: This study confirmed the correlation between overall score, systemic symptoms, social and emotional domains related to HRQOL of patients with Crohn's disease supporting the reliability of IBDQ-32 to assess HRQOL in patients suffering from this condition.

9. CROATIAN SUMMARY

Naslov: Kvaliteta života povezana sa zdravljem u pacijenata s Crohnovom bolesti

Ciljevi: Kvaliteta života je značajno pogođena u pacijenata s Crohnovom bolesti jer je ta bolest kronična, remitentna i nepredvidiva, a negativno utječe na svakodnevne aktivnosti. Cilj ovog istraživanja bio je ustanoviti kvalitetu života povezanu sa zdravljem u pacijenata s Crohnovom bolesti.

Ispitanici i metode: U istraživanje je uključeno ukupno 30 pacijenata kojima je dijagnosticirana Crohnova bolest te im je podijeljen *Inflammatory Bowel Disease Questionnaire* (IBDQ-32) kojeg sačinjavaju 32 čestice kako bi se procijenila njihova kvaliteta života i karakteristike povezane sa Splitsko-dalmatinskom županijom..

Rezultati: Nije pronađena statistički značajna razlika među pacijentima u kojih je bolest aktivna i u kojih bolest nije aktivna. Percepcija kvalitete života u ispitanika je pozitivno korelirala s ukupnim zbirom ($r=0,506$; $P=0,004$) te je također pronađena pozitivna korelacija između kvalitete života i gastrointestinalnih simptoma, ali nije bila značajna. Domene sustavni simptomi ($r=0,629$; $P<0,001$), emotivna uključenost ($r=0,588$; $P<0,001$), zajedno s društvenim utjecajem ($r=0,458$; $P<0,011$) su pozitivno korelirale sa samo-percepcijom kvalitete života.

Zaključci: Ovo istraživanje je potvrdilo korelaciju između ukupnog zbira, domena sustavni simptomi i emotivna uključenost povezanih s kvalitetom života u pacijenata s Crohnovom bolesti što potvrđuje pouzdanost IBDQ-32 u procjeni kvalitete života u pacijenata koji boluju od ove bolesti.

10. CURRICULUM VITAE

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