UNIVERSITY OF SPLIT

SCHOOL OF MEDICINE

Alvaro Gomez Diaz

ASSESMENT OF QUALITY OF LIFE IN PATIENTS WITH ULCERATIVE COLITIS

Diploma thesis

Academic year:

2017/2018

Mentor:

Assist. Prof. Joško Božić, MD, PhD

Split, July 2018

UNIVERSITY OF SPLIT

SCHOOL OF MEDICINE

Alvaro Gomez Diaz

ASSESMENT OF QUALITY OF LIFE IN PATIENTS WITH ULCERATIVE COLITIS

Diploma thesis

Academic year:

2017/2018

Mentor:

Assist. Prof. Joško Božić, MD, PhD

Split, July 2018

TABLE OF CONTENTS

1. INTRODUCTION

Inflammatory bowel disease (IBD) is a spectrum of chronic immune-mediated intestinal conditions which has slowly become a worldwide healthcare problem with increasing incidence. Ulcerative colitis (UC) and Crohn's disease (CD) represent the two distinctive types of IBD. However, 4% of IBD cases cannot be defined as either CD or UC (1).

The highest incidence rates and prevalence of UC and CD have been reported from northern Europe, the UK and North America. In low-incidence areas like southern Europe, Asia and other developing countries the incidence is rising (2).

CD causes transmural inflammation and any part of the gastrointestinal tract can be affected. However, most commonly affected parts of gastrointestinal tract in patients with CD are terminal ileum or perianal region. The inflammation in CD is not necessarily confluent, frequently areas of relatively normal mucosa can be found. Furthermore, transmural nature of the inflammation in CD may lead to fibrosis and formation of strictures and fistulas. IBD is frequently accompanied with extra intestinal manifestations involving the joints, skin or eyes (1,3,4).

IBD has been associated with many comorbidities such as psychiatric disorders, skin conditions and neurologic disorders. Anxiety disorder and depression are considerably more prevalent in IBD patients than in the general population (5).

1.1. Definition

UC is an idiopathic chronic disorder characterized by a mucosal inflammation of the colon. The disorder begins in the rectum and extents proximally in a continuous pattern. The portion of the colon affected can vary. Some individuals have inflammation that is limited to the rectum (ulcerative proctitis). In contrast, other patients have a more proximal disease. Pancolitis is the term referred to UC in which the entire colon is affected (6). Alternating periods of remission and relapse characterize UC. Furthermore, active forms of UC can range from mild to moderate or severe disease (7,8).

1.2. Epidemiology

The incidence of UC is higher than the incidence of CD. The highest incidence and prevalent rates of UC have been observed in North America and northern Europe. Furthermore, UC is characterized by having a bimodal pattern of incidence. The main peak of onset is in between 15 and 30 years of age, and the second smaller peak is in between 50 and 70 years of age. The prevalence of UC is very similar between men and women, unlike CD,

which has a higher incidence in women. However, some studies have shown that UC has a slight predilection for men. In the US, the amount of patients with UC did not vary significantly by race. Smokers and patients who have had an appendectomy were less likely to develop the disease (2,7,9).

Recently published article by Despalatović *et al.* investigated the epidemiological trends of IBD in Split-Dalmatia County from 2006 to 2014. During this period 414 individuals older than 18 years were diagnosed with IBD. Moreover, 68.5% of these patients were diagnosed with UC, 47% of which were females (10).

1.3. Pathophysiology

The exact pathogenesis of UC remains mostly unknown. However, numerous studies concluded that in genetically predisposed individuals composition of intestinal flora, epithelial cell barrier function and immune responses interact to create a state of dysregulated mucosal immune function (1).

Several studies have shown that microorganisms are likely to have a role in the development of UC. Animal studies have showed that colitis did not develop in sterile conditions but it was provoked after introduction of commensal bacteria. Moreover, it was detected that when stool was diverted from the active mucosal inflammation, like in an ileostomy, the inflammation was reduced (11).

Some recent studies showed that UC is a disease product of a dysregulated innate immune system which activates T cells and a humoral response. Antigen presenting cells produce IL-23 which activates Th17 (11). Immunologic background of UC (and both CD) pathophysiology is presented in Figure 1.

Figure 1. Proposed pathogenesis of UC

SOURCE: MacNaughton WK, Sharkey KA. Pharmacotherapy of Inflammatory Bowel Disease. In: Brunton LL, Hilal-Dandan R, Knollman BC, editors. The pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill; 2018. p. 945-54.

1.4. Risk factors

The etiology of IBD is still mostly unknown. However, it includes a complex interaction between environmental factors, genetics and immune responses.

Most important independent risk factor is a family history of IBD (12). It has been shown that 5.7 - 15.5% of patients with UC have a first degree family member with the same condition. Additionally, studies conducted among Ashkenazi Jews showed that the rates of UC were 3 to 5 times higher than in other ethnicities. Finally, recent studies revealed that the environmental factors could influence genetically predisposed individuals (7).

Several environmental factors have been recognized as either triggers or protective factors for UC. Among the investigated factors, only appendectomy and cigarette smoking had a well-known influence on the risk of developing UC. According to previously published data, cigarette smoking is protective against UC compared with the individuals that do not

smoke. Furthermore, smokers tend to have a milder disease course than patients who do not smoke. Moreover, it was observed that disease activity was increased in patients who ceased smoking (13,14).

Several studies associated gastrointestinal infections (*Salmonella*, *Campylobacter*, *Shigella* etc.) to an increased risk of UC development (15,16).

1.5. Diagnosis

Diagnosis of UC is based on the patient's medical history and clinical symptoms. However, it should be confirmed by endoscopic, histologic, laboratory, radiologic and serological examinations (17,18).

Clinical, endoscopic and pathological features of UC are presented in Table 1. According to previously published guidelines, before the diagnosis is made, other causes of diarrhea should be excluded.

Most common other causes can be non infectious (e.g. tumors, microscopic colitis, drug induced diarrhea) and infectious diseases (1,17). CD may sometimes have a similar presentation to UC so some of the most commonly found features that can distinct UC and CD are: presence of perianal disease, absence of rectal inflammation and granulomas on endoscopy (19).

Chronic diarrhea and bleeding can be induced by medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), retinoic acid and mycophenolate (20). Infectious colitis can have similar endoscopic appearance and clinical presentation as UC. Patients who are presenting with this clinical manifestations should be excluded with stool culture, and biopsies of the colon (3).

Inflammation usually starts in the rectum and extends proximally in a continuous pattern limited to a part of, or to the entire colon. However, some individuals with left-sided colitis or proctitis have rectal sparing and cecal patch of inflammation. The extent of the mucosal inflammation should be assessed at diagnosis in order to select an appropriate treatment (1,11,19).

Apart from disease diagnosis, endoscopy in IBD plays a major role in prediction of disease severity and extent (i.e. mucosal healing) for tailored patient management and for screening of colitis-associated cancer and its precursor lesions. Classification is based on the number of stools per day and systemic symptoms of inflammation, such as tachycardia and fever (12,19,21).

Table 1. Diagnosis of ulcerative colitis

Clinical features	Endoscopic features	Pathological features
Rectal bleeding	Loss of vascular pattern	Distortion of crypt architecture
Diarrhea	Erythema	Crypt abcesses
Urgency	Granularity	Lamina propria cellular infiltrate
Tenesmus	Friability	Shortening of the crypts
Abdominal pain	Erosions	Mucin depletion
Fever (severe cases)	Ulcerations	Lymphoid aggregates
Extra intestinal manifestation	Spontaneous bleeding	Erosion or ulceration

SOURCE: Ordas I, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. Lancet. 2012;380(9853):1606-19.

1.6. Clinical presentation

In patients with UC clinical symptoms usually develop over time, rather than suddenly. UC can be debilitating and sometimes it can lead to life-threatening complications. Depending on the severity of the inflammation and where it occurs signs and symptoms may vary. The main symptoms include: bloody diarrhea (sometimes containing pus), abdominal pain, cramps, urgency to defecate, tenesmus, rectal bleeding, weight loss, fatigue and fever (1).

In children diagnosed with UC limited has often been observed. Most people with UC have mild to moderate manifestations. The course of UC may vary, with some patients having long periods of remission (22,23).

UC is classified according to the extent of the involvement. This classification includes: proctitis (when the disease is confined to the rectum), proctosigmoiditis, left sided colitis (affecting descending colon up to the splenic flexure) and pancolitis (extending from the rectum to the caecum) (24).

The disease course can be affected with several factors. For instance, patients with late onset UC (diagnose at age 50 years or older) were more likely to achieve clinical remission

without the need for use of corticosteroids, in comparison with patients that had early onset UC (diagnosed between ages 18 and 30 years) (25).

Furthermore, another important factor is the appendectomy. Patients who underwent appendix removal at a younger age, and before they were diagnosed with UC, had lower risk of hospitalizations and need for colectomy, in comparison with the patients who did not have appendectomy surgery (26).

Patients with UC may present with extra intestinal manifestations. Several studies reported that the frequency of these complications (outside the colon) is somewhere between 6 and 47% and they include: aphtous ulcers in the mouth, iritis, uveitis, episcleritis, seronegative arthritis, ankylosing spondilitis, sacroilitis, erythema nodosum (an inflammation of the subcutaneous tissue involving lower extremities), pyoderma gangrenosum (painful ulceration of the skin), deep venous thrombosis, autoimmune hemolitic anemia, clubbing fingers and primary sclerosing cholangitis (27).

The most frequently reported extra intestinal manifestation among UC patients has been arthritis. Peripheral arthritis and ankylosing spondylitis are the most common types observed in UC patients. Previous studies associated UC patients that use corticosteroids with lower bone mineral density and higher risks of osteoporosis and fragility fractures (3,28).

Patients that complain about burning, redness or itching sensation of the eyes should be referred to an ophthalmologist due to possible extra intestinal manifestations of UC such as uveitis and episcleritis (29).

1.7. Treatment

Therapeutic agents of UC include aminosalicylates, corticosteroids, thiopurines, cyclosporine and biological agents. In spite of many pharmacological approaches, there is still a need for implementation of newer therapies, because the existing therapies achieve low remission rate or unbearable side effects (30) .

However, recently published systematic review by Kokkindis *et al.* concluded that novel biological therapies as vedolizumab and gomumab showed promising efficacy and had satisfactory adverse effects profile. Further studies are needed to confirm the findings presented in this study (31).

According to Clinical practice guidelines published in 2015, 5-aminosalicylic acid (5-ASA) has been recognized as the first line therapy for mild to moderate UC. In patients with active proctitis, 5-ASA for rectal application has been recommended. Enemas are recommended in patients with active left sided UC, and oral form is recommended to patients

in whom disease has extended beyond proctitis. Clinicians are advised to evaluate lack of response to 5-ASA in 4 to 8 weeks in order to determine if there is a need for therapy modification. If 5-ASA does not induce remission, patients should use corticosteroids (8). Furthermore, adverse effects with 5-ASA are rare, and all patients with UC who tolerate this drug, should use 5-ASA (32).

Corticosteroids should be advised to patients who failed to achieve remission with other medication. However, long term use of corticosteroids is not safe and should not be used to maintain the remission (30). If the steroid resistance in UC occurs, aminosalicylates, the immunomodulators (azathioprine, 6-mercaptopurine or methotrexate), adalimumab, infliximab or calcineurin inhibitors such as cyclosporine or tacrolimus can be administered (33).

Medical therapy cannot always achieve an improvement in patients with severe acute or chronic colitis. For those patients surgical intervention is the next step. The most common surgical approach in the setting of acute and fulminant UC is total colectomy with a Hartman pouch. Posteriorly this can be converted into a total proctocolectomy with end -ileostomy or an ileal pouchanal anastomosis. Majority of the patients prefer the ileal poucheanal anastomisis because it keeps the flow of stool through the anus avoiding a permanent ostomy (34,35,36).

Perforation, toxic megacolon or carcinoma are absolute indications for surgical intervention in patients with UC. Hartman's pouch is well tolerated by majority of the patients who undergo surgery. However, 50% of the patients will develop pouchitis, and about 10 to 12% will develop chronic pouchitis (37,38).

Usually the patients with an ileal poucheanal anastomosis will experience 4 to 6 bowel movements a day but this can be efficiently reduced by the use of loperamide and fiber supplements (37,38).

A literature review performed recently showed that the patients quality of life 1 year after surgery was equivalent to that in the general population. Even though there are potential benefits of surgery, colectomy is associated with a 54% of reoperation due to postsurgical complications (39,40).

1.9. Complications of UC

Acute complications of UC include lesions, severe bleeding, fulminant colitis, toxic megacolon and perforation. Bleeding can occur in any stage of the UC, and it has usually been reported in up to 3% of patients. Urgent colectomy is necessary treatment in patients

with massive hemorrhage. However, lesions in UC patients can occur even after colectomy (41).

Fulminant colitis can lead to the development of toxic megacolon. Toxic megacolon represents a life threatening complication of mostly infectious or inflammatory conditions of the colon. Recently, the epidemiology has shifted toward infectious origins, particulary due to an increase of *Clostridium difficile*-associated colitis associated with extensive use of antibiotics (42,43).

Furthermore, toxic megacolon is usually associated with colonic diameter around 6 cm or cecal diameter around 9 cm and systemic toxicity. Untreated toxic megacolon can often lead to perforation and increased mortality of patients with UC (44).

Cronic complications of UC include strictures and development of colorectal cancer. Frequent episodes of inflammation and muscle hypertrophy are the main causes of the benign strictures in patients with UC. Strictures can most often occur in the rectosigmoid segment of the colon and in some cases it can lead to the obstruction of the lumen (45).

Additionally, strictures should be evaluated by endoscope with a biopsy, to exclude the possible malignancy of the strictures. If the strictures cannot be completely evaluated for exclusion of malignancy, and if the patients report recurrent obstruction symptoms, surgical intervention should be strongly considered (46).

Patients with UC have higher risk for developing colorectal cancer. Numerous studies confirmed this association. Colorectal cancer has been recognized as one of the most serious consequences of UC. Previous studies have shown that incidence of colorectal cancer is higher in UC patients who were younger at the time they were diagnosed, had greater anatomical extent of the disease and family history of colorectal cancer. In order to reduce the risk of colorectal cancer, and mortality of patients, patients are recommended to obtain regular colonoscopy examinations. Several studies have concluded that 5-aminosalicylates might prevent colorectal cancer and should be first line therapy in high risk patients (21,47,48).

1.8. Quality of life in UC

In some recent studies it was shown that adaptation to UC is very complex and that pharmacotherapy alone is most often insufficient to regain and maintain a "normal life". Individuals with UC suffer from recurrent clinical signs and symptoms, like rectal bleeding, anemia, profuse diarrhea, fecal urgency and abdominal pain (49).

Patients with IBD experience concerns that go beyond clinical symptoms of their disease; anxiety and depression due to a lack of control of their body functions, fear of disease

progression, hospitalization and surgery. They also report many limitations in the ability to enroll in social or recreational activities, school, work and subsequent difficulties for establishing relationships with others due to the constant urge to access the toilet (50,51).

Previously published survey reported that following colectomy, UC individuals have a quality of life equivalent with that of the general population (52,53). However, patients should accept the potential risks of a challenging surgical intervention to remove the colon, its postoperative complications, infertility, lifelong stomy and pouchitis. Moreover, this procedure may heal individuals with colonic disease but it does not completely eliminate symptoms of incontinence and fecal urgency (53,54).

2. OBJECTIVES

OBJECTIVES:

1. Determine the differences in quality of life between UC patients and control group

2. Determine the differences in quality of life between patients with active and not active UC

HYPOTHESIS:

1. Patients with UC will have reduced quality of life when compared to control group

2. Patients with active disease will report reduced quality of life compared to patients who are in remission

3. SUBJECTS AND METHODS

3.1. Study design

This cross-sectional, questionnaire-based study was conducted at Department of Gastroenterology and Hepatology (University Hospital of Split) and Department of Pathophysiology (University of Split School of Medicine). Study was performed from December 2017 to May 2018. All participants were informed about procedures, course and aim of this study.

3.2. Ethical considerations

Written informed consent was obtained from all individual participants included in the study. The study protocol was approved by the Ethics Committee of the University of Split School of Medicine and University Hospital of Split. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

3.3. Subjects

This study included 30 patients with ulcerative colitis and 30 age and sex matched control subjects. The diagnosis is based on the history, as well as clinical, radiological, endoscopic and histological features in accordance with European Crohn's and Colitis Organisation (ECCO) consensus on the diagnosis and management of ulcerative colitis (55). Remission is defined as complete resolution of symptoms self-reported from the patient. Information about disease duration was taken from patients' medical documentation.

Subjects included in the study underwent a detailed medical history interview, physical examination, and anthropometric measurements. Body height and weight were measured followed by the calculation of body mass index (BMI).

3.4. HRQoL assessment

Health-related quality of life (HRQoL) was measured by Medical Outcomes Study Short Form-36 (SF-36) questionnaire which has been well established instrument for HRQoL assessment. SF-36 is a multifunctional, non-disease specific, 36-item health survey that evaluates 8 domains of health providing an overall assessment of HRQoL (56).

Health aspects that are being valued are physical functioning (10 items), role limitations due to physical health (4 items), role limitations due to emotional health (3 items), energy/fatigue (4 items), emotional well-being (5 items), social functioning (2 items), bodily

pain (2 items) and general health perception (5 items). Each item is scored on a 0 to 100 scale so that the lowest and highest possible scores are 0 and 100, respectively. Furthermore, items in the same scale are averaged together to create the 8 scale scores, where higher score indicates better HRQoL (57).

3.5. Statistical analysis

Statistical software MedCalc ver. 11.5.1.0 for Windows (MedCalc Software, Ostend, Belgium) was used for statistical data analysis. Data were expressed as means ± standard deviation for continuous variables and as whole numbers and percentage for categorical variables. Kolmogorov-Smirnov test has been used for normality of data distribution. Student t-test was used for comparison of different domains of SF-36 between UC and control group. Pearson's correlation coefficient was used for assessment of correlation between SF-36 variables and other variables. The statistical significance was defined as $P<0.05$.

4. RESULTS

Table 2 describes the baseline parameters which were measured in patients with UC and in control group. Both groups consisted of participants of both genders with no significant difference in anthropometric parameters between the groups. Less smoker individuals were observed in UC group in comparison to the control group. However, this finding was not considered statistically significant.

Table 2. Subjects' characteristics

SF-36 domain	UC group (N=30)	Control group (N=30)	P*
Age (years)	40.4±14.0	38.6±11.3	0.585
Gender			
Men (N)	18 (60%)	15 (50%)	0.440†
Women (N)	12 (40%)	15 (50%)	
Body weight (kg)	78.9±17.4	83.1±16.6	0.340
Body height (cm)	177.6±8.5	178.3±10.0	0.782
BMI (kgm^{-2})	24.8±4.0	26.0±3.4	0.250
Smokers (N)	2 (6.7%)	7 (23.3%)	0.145‡

Data is presented as mean±standard deviation or number (percentage) where appropriate
*students' t-test for independent samples
†chi-square test
‡ Fischer's exact test

Distribution of patients relative to the duration of the disease given in years is presented in Figure 2. Most of the patients were diagnosed with ulcerative colitis up to 10 years prior to the study.
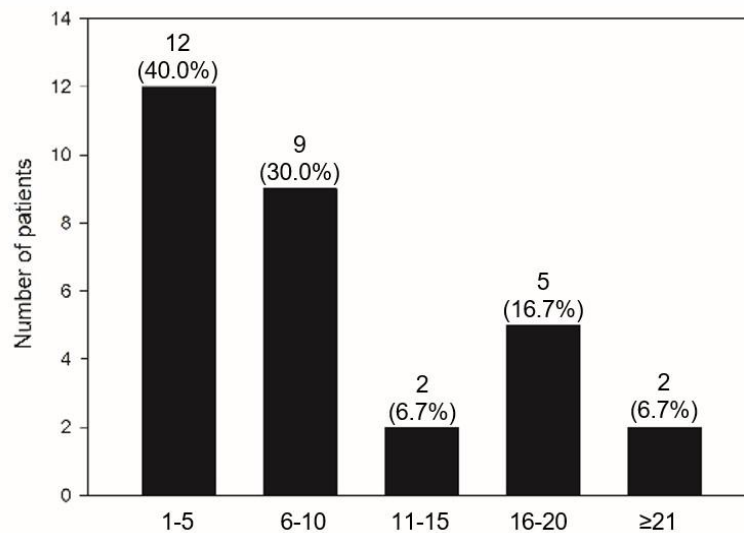

Figure 2. Distribution of patients relative to the duration of the disease in years

The results of SF-36 questionnaire are presented in Table 3. Interestingly, the only significant differences between groups were observed in 2 domains, domain role limitations due to physical health and domain general health. However, mean values in UC group for all 8 domains were considerably lower than the mean values in control group.
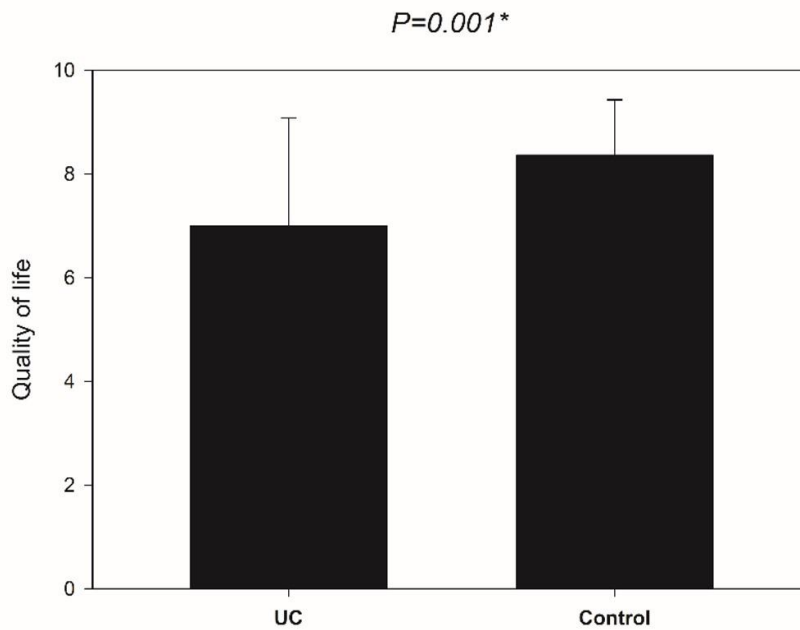
Table 3. SF-36 domains

SF-36 domain	UC group (N=30)	Control group (N=30)	*P**
Physical functioning	81.7±21.0	88.8±16.1	0.144
Role limitations due to physical health	70.8±41.6	94.2±11.2	0.004
Role limitations due to emotional problems	80.0±32.3	86.7±20.7	0.345
Energy/fatigue	58.0±17.5	65.0±16.7	0.118
Emotional well-being (mental health)	68.0±13.2	73.3±12.2	0.108
Social functioning	77.9±21.2	85.4±15.8	0.125
Pain	77.6±18.3	85.3±16.3	0.092
General health	52.7±19.6	72.3±16.8	<0.001

Data is presented as mean±standard deviation
*students' t-test for independent samples

Self-assessment of quality of life is presented in Figure 3. Patients with ulcerative colitis perceived their quality of life as significantly lower than control patients.

*students' t-test for independent samples
Figure 3. Self-assessment of quality of life in patients with ulcerative colitis (UC) (N=30) compared to healthy controls (N=30)

Table 4. Ulcerative colitis duration correlation to SF-36 domains

SF-36 domain	r	*P**
Physical functioning	-0.519	0.003
Role limitations due to physical health	-0.434	0.017
Role limitations due to emotional problems	-0.104	0.585
Energy/fatigue	-0.051	0.789
Emotional well-being (mental health)	-0.195	0.303
Social functioning	-0.182	0.337
Pain	-0.334	0.071
General health	-0.358	0.050

* Pearson correlation test

Statistically significant negative correlation was found between UC duration and 3 domains of SF-36 questionnaire: physical functioning (r=-0.519, P=0.003), role limitations due to physical health (r=-0.434, P=0.017) and general health (r=-0.358, P=0.050) (Table 4). There was no significant correlation observed between disease duration and other domains of the SF-36 questionnaire.

Quality of life, as measured with SF-36 questionnaire, remains similar among patients regardless of their disease activity. There were no significant differences observed in any SF-36 domain, among patients with active UC and patients whose disease is currently not active (Table 5).

Table 5. SF-36 domains with reference to disease activity

SF-36 domain	UC active (N=18)	UC not active (N=12)	P*
Physical functioning	90.0 (80.0-100.0)	80.0 (72.5-100.0)	0.519
Role limitations due to physical health	100.0 (25.0-100.0)	100.0 (37.5-100.0)	0.962
Role limitations due to emotional problems	100.0 (66.7-100.0)	100.0 (66.6-100.0)	0.659
Energy/fatigue	55.0 (45.0-65.0)	55.0 (47.5-70.0)	0.848
Emotional well-being (mental health)	66.0 (60.0-76.0)	66.0 (60.0-72.0)	0.610
Social functioning	75.0 (50.0-100.0)	87.5 (68.8-100.0)	0.561
Pain	80.0 (67.5-90.0)	77.5 (61.3-90.0)	0.482
General health	57.5 (45.0-75.0)	42.5 (30.0-60.0)	0.168

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

5. DISCUSSION

UC is a disease affecting millions of patients worldwide with a significant impact on their quality of life (58). Furthermore, with the introduction of novel biological treatments, management of UC is costly for health care systems (59). The present study was made in order to confirm the recent investigations concerning this health issue by comparing quality of life of patients with UC and healthy controls at the Department of Gastroenterology and Hepatology, University Hospital of Split.

In the present study differences were observed in results of SF-36 questionnaire domains analysis between patients with UC and control group. UC patients scored lower in all domains of SF-36 questionnaire which translates to lower quality of life in patients with UC. This finding was observed in previous studies (60,61,62). However, not all of the differences between groups were considered significant. The largest differences were observed in domains general health and role limitations due to physical health. The first domain consists of the questions that examine if patients are satisfied with their health in general and how they perceive their health in comparison with other people. Furthermore, upon self-assessment, patients with UC considered their quality of life to be significantly lower than controls.

Results of the present study suggest that patients with UC considered their health considerably inferior in comparison with the general health of people who are not suffering from the UC. Similar findings were observed in previously published studies (63,64). Interestingly, significant difference was found in domain Role limitations due to physical health, but not in domains Role limitations due to emotional problems, Emotional well-being or Social functioning. Previous studies have identified fecal incontinence and perianal disease as quality of life determining factors for patients with IBD (65). This study included more patients with active disease, than patients in remission, however patients reported no significant influence on the disease on their social or emotional well-being compared to controls.

One study conducted in Norway that included patients with similar anthropologic characteristics showed similar outcomes. Moreover, lower scores in SF-36 questionnaire of UC patients were observed only in the general health domain, in comparison to the general population (66).

The second domain, role limitations due to physical health, consists of the questions that examine if patients were limited in the amount of time spent on activities or if they were limited in kind of activities. Our results propose that UC has the capacity to restrict patients, and make them unable to accomplish their daily activities. Interestingly, none statistically significant differences were observed in other domains.

23

However, study from Hjortswang *et al.* conducted on 300 patients with UC obtained the opposite results than the ones observed in the present study. The researchers concluded that patients' health related quality of life was primarily impaired in the psychological and social domains and to a much lesser extent in physical domains (67).

The present study has showed that there is a negative correlation in between the duration of UC and SF-36 domains. This finding propose that patients who suffered from the disease for a longer period had a considerably lower self-perceived quality of life. However, this correlation was statistically significant in only 3 domains. The most significant finding was observed in the domain of physical functioning. The patients who were suffering from the disease for a longer period of time perceived more difficulties in accomplishing vigorous or moderate activities, lifting, climbing stairs, bending, walking and bathing or dressing themselves. This finding is subject to bias, as inevitably patients with longer duration of disease tend to be older in general.

The results of the present study did not show any difference between patients with active UC and patients with not active UC. However, this finding was unexpected since there is an increasing evidence that patients with active disease have significantly lower scores for all 8 domains of SF-36 compared to patients who achieved a remission (63,64,68,69).

However, study from McMullan *et al.* described how particular patients with severe UC were capable to maintain a "sense of normality in life" probably due to the ability to adapt to their newly established condition and presence of social support (70). Furthermore, a study conducted among pediatric patients with IBD demonstrated that parents and medical staff tend to underestimate the quality of life of children with IBD (71). It is possible that both medical staff and general population tend to underestimate the quality of life in adult patients with IBD.

Previously conducted studies reported that in patients with IBD health literacy and education were significantly associated with self-perceived quality of life and health status (72). This study did not collect education data and did not asses health literacy in patients therefore the obtained results might be limited. However, due to the fact that in the present study significant difference was found only in domains role limitations due to physical health and general health we do not believe that patients included in this study were likely to underestimate their quality of life. However, a greater sample size might yield more accurate results that could be comparable to the results of previous studies. A greater sample size is needed to assess the differences in quality of life of patients with active UC and those with not active UC.

6. CONCLUSION

1. Patients with UC had a lower score in all SF-36 domains compared to the control group with statistical significance in domains of role limitations due to physical health and general health

2. Statistically significant correlations between duration of the disease and SF-36 questionnaire were observed in domains of physical functioning, role limitations due to physical health and general health

3. There was no significant difference in patients' self-perceived quality of life according to activity of the disease

4. Patients with UC had significantly lower self-perceived quality of life compared with control group

7. REFERENCES

1.   Friedman S, Blumberg RS. Inflammatory Bowel Disease. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalazo J, editors. Harrison´s Principles of Internal Medicine. 18th ed. New York: McGraw-Hill; 2012. p. 2477-95.

2.   Loftus EV, Jr. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. Gastroenterology. 2004;126:1504-17.

3.   Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. Lancet. 2007;369:1641-57.

4.   Boyapati R, Satsangi J, Ho GT. Pathogenesis of Crohn's disease. F1000Prime Rep. 2015;7:44.

5.   Mikocka-Walus A, Knowles SR, Keefer L, Graff L. Controversies Revisited: A Systematic Review of the Comorbidity of Depression and Anxiety with Inflammatory Bowel Diseases. Inflamm Bowel Dis. 2016;22:752-62.

6.   Silverberg MS, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol. 2005;19 Suppl A:5A-36A.

7.   Ordas I, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. Lancet. 2012;380:1606-19.

8.   Bressler B, Marshall JK, Bernstein CN, Bitton A, Jones J, Leontiadis GI, et al. Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: the Toronto consensus. Gastroenterology. 2015;148:1035-58.

9.   Bernstein CN, Rawsthorne P, Cheang M, Blanchard JF. A population-based case control study of potential risk factors for IBD. Am J Gastroenterol. 2006;101:993-1002.

10. Despalatovic BR, Bratanic A, Radic M, Jurisic Z, Tonkic A. Epidemiological trends of inflammatory bowel disease (IBD) in Split-Dalmatia County, Croatia from 2006 to 2014. Eur J Intern Med. 2017;46:e17-9.

11. Lichenstein GR. Inflammatory bowel disease. In: Goldman L, Schafer AI, editors. Goldman-Cecil Medicine. 25th ed. Philadelphia: Elsevier Saunders; 2016. p. 935-42.

12. Orholm M, Munkholm P, Langholz E, Nielsen OH, Sorensen TI, Binder V. Familial occurrence of inflammatory bowel disease. N Engl J Med. 1991;324:84-8.

13. Beaugerie L, Massot N, Carbonnel F, Cattan S, Gendre JP, Cosnes J. Impact of cessation of smoking on the course of ulcerative colitis. Am J Gastroenterol. 2001;96:2113-6.

14. Mahid SS, Minor KS, Soto RE, Hornung CA, Galandiuk S. Smoking and inflammatory bowel disease: a meta-analysis. Mayo Clin Proc. 2006;81:1462-71.

15. Tripathi MK, Pratap CB, Dixit VK, Singh TB, Shukla SK, Jain AK, et al. Ulcerative Colitis and Its Association with Salmonella Species. Interdiscip Perspect Infect Dis. 2016;2016:5854285.

16. Adams SM, Bornemann PH. Ulcerative colitis. Am Fam Physician. 2013;87:699-705.

17. Conrad K, Roggenbuck D, Laass MW. Diagnosis and classification of ulcerative colitis. Autoimmun Rev. 2014;13:463-6.

18. Tontini GE, Vecchi M, Pastorelli L, Neurath MF, Neumann H. Differential diagnosis in inflammatory bowel disease colitis: state of the art and future perspectives. World J Gastroenterol. 2015;21:21-46.

19. Laass MW, Roggenbuck D, Conrad K. Diagnosis and classification of Crohn's disease. Autoimmun Rev. 2014;13:467-71.

20. Haschke M. Drugs and diarrhea. Therapeutische Umschau. 2014;71:565-9.

21. Rogler G. Chronic ulcerative colitis and colorectal cancer. Cancer Lett. 2014;345:235-41.

22. Kaser A, Zeissig S, Blumberg RS. Inflammatory bowel disease. Annu Rev Immunol. 2010;28:573-621.

23. Podolsky DK. Inflammatory bowel disease. N Engl J Med. 2002;347:417-29.

24. Magro F, Langner C, Driessen A, Ensari A, Geboes K, Mantzaris GJ, et al. European consensus on the histopathology of inflammatory bowel disease. J Crohns Colitis. 2013;7:827-51.

25. Ha CY, Newberry RD, Stone CD, Ciorba MA. Patients with late-adult-onset ulcerative colitis have better outcomes than those with early onset disease. Clin Gastroenterol Hepatol. 2010;8:682-7.

26. Myrelid P, Landerholm K, Nordenvall C, Pinkney TD, Andersson RE. Appendectomy and the Risk of Colectomy in Ulcerative Colitis: A National Cohort Study. Am J Gastroenterol. 2017;112:1311-9.

27. Vavricka SR, Brun L, Ballabeni P, Pittet V, Prinz Vavricka BM, Zeitz J, et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. Am J Gastroenterol. 2011;106:110-9.

28. Khan N, Abbas AM, Almukhtar RM, Khan A. Prevalence and predictors of low bone mineral density in males with ulcerative colitis. J Clin Endocrinol Metab. 2013;98:2368-75.

29. Eugene C. Ulcerative colitis practice guidelines in adults. Clin Res Hepatol Gastroenterol. 2012;36:10-2.

30. MacNaughton WK, Sharkey KA. Pharmacotherapy of Inflammatory Bowel Disease. In: Brunton LL, Hilal-Dandan R, Knollman BC, editors. The pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill; 2018. p. 945-54.

31. Kokkinidis DG, Bosdelekidou EE, Iliopoulou SM, Tassos AG, Texakalidis PT, Economopoulos KP, et al. Emerging treatments for ulcerative colitis: a systematic review. Scand J Gastroenterol. 2017;52:923-31.

32. Hauso O, Martinsen TC, Waldum H. 5-Aminosalicylic acid, a specific drug for ulcerative colitis. Scand J Gastroenterol. 2015;50:933-41.

33. Manz M, Vavricka SR, Wanner R, Lakatos PL, Rogler G, Frei P, et al. Therapy of steroid-resistant inflammatory bowel disease. Digestion. 2012;86 Suppl 1:11-5.

34. Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. 2010;105:501-23.

35. Dignass A, Lindsay JO, Sturm A, Windsor A, Colombel JF, Allez M, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. J Crohns Colitis. 2012;6:991-1030.

36. Targownik LE, Singh H, Nugent Z, Bernstein CN. The epidemiology of colectomy in ulcerative colitis: results from a population-based cohort. Am J Gastroenterol. 2012;107:1228-35.

37. Shen B. Pouchitis: what every gastroenterologist needs to know. Clin Gastroenterol Hepatol. 2013;11:1538-49.

38. Gorgun E, Remzi FH. Complications of ileoanal pouches. Clin Colon Rectal Surg. 2004;17:43-55.

39. Bernstein CN, Ng SC, Lakatos PL, Moum B, Loftus EV, Jr. A review of mortality and surgery in ulcerative colitis: milestones of the seriousness of the disease. Inflamm Bowel Dis. 2013;19:2001-10.

40. Feuerstein JD, Curran T, Alosilla M, Cataldo T, Falchuk KR, Poylin V. Mortality Is Rare Following Elective and Non-elective Surgery for Ulcerative Colitis, but Mild Postoperative Complications Are Common. Dig Dis Sci. 2018;63:713-22.

41. Uchino M, Matsuoka H, Bando T, Hirata A, Sasaki H, Hirose K, et al. Clinical features and treatment of ulcerative colitis-related severe gastroduodenitis and enteritis with massive bleeding after colectomy. Int J Colorectal Dis. 2014;29:239-45.

42. Autenrieth DM, Baumgart DC. Toxic megacolon. Inflamm Bowel Dis. 2012;18:584-91.

43. Schaffler H, Breitruck A. Clostridium difficile - From Colonization to Infection. Front Microbiol. 2018;9:646.

44. Miniello S, Marzaioli R, Balzanelli MG, Dantona C, Lippolis AS, Barnaba D, et al. Toxic megacolon in ulcerative rectocolitis. Current trends in clinical evaluation, diagnosis and treatment. Ann Ital Chir. 2014;85:45-9.

45. Feuerstein JD, Cheifetz AS. Ulcerative colitis: epidemiology, diagnosis, and management. Mayo Clin Proc. 2014;89:1553-63.

46. Ribiere S, Bouhnik Y. Management of intestinal complications in inflammatory bowel diseases. Rev Prat. 2014;64:1249-55.

47. Yashiro M. Ulcerative colitis-associated colorectal cancer. World J Gastroenterol. 2014;20:16389-97.

48. Shah SC, Ten Hove JR, Castaneda D, Palmela C, Mooiweer E, Colombel JF, et al. High Risk of Advanced Colorectal Neoplasia in Patients With Primary Sclerosing Cholangitis Associated With Inflammatory Bowel Disease. Clin Gastroenterol Hepatol. 2018;16:1106-13.

49. Ford AC, Moayyedi P, Hanauer SB. Ulcerative colitis. BMJ. 2013;346:f432.

50. Sammut J, Scerri J, Xuereb RB. The lived experience of adults with ulcerative colitis. J Clin Nurs. 2015;24:2659-67.

51. McCormick JB, Hammer RR, Farrell RM, Geller G, James KM, Loftus EV, Jr., et al. Experiences of patients with chronic gastrointestinal conditions: in their own words. Health Qual Life Outcomes. 2012;10:25.

52. Carmon E, Keidar A, Ravid A, Goldman G, Rabau M. The correlation between quality of life and functional outcome in ulcerative colitis patients after proctocolectomy ileal pouch anal anastomosis. Colorectal Dis. 2003;5:228-32.

53. Holubar S, Hyman N. Continence alterations after ileal pouch-anal anastomosis do not diminish quality of life. Dis Colon Rectum. 2003;46:1489-91.

54. Waljee A, Waljee J, Morris AM, Higgins PD. Threefold increased risk of infertility: a meta-analysis of infertility after ileal pouch anal anastomosis in ulcerative colitis. Gut. 2006;55:1575-80.

55. Dignass A, Eliakim R, Magro F, Maaser C, Chowers Y, Geboes K, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. J Crohns Colitis. 2012;6:965-90.

56. McHorney CA, Ware JE, Jr., Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. 1994;32:40-66.

57. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30:473-83.

58. da Silva BC, Lyra AC, Rocha R, Santana GO. Epidemiology, demographic characteristics and prognostic predictors of ulcerative colitis. World J Gastroenterol. 2014;20:9458-67.

59. Lee JK, Tang DH, Mollon L, Armstrong EP. Cost-effectiveness of biological agents used in ulcerative colitis. Best Pract Res Clin Gastroenterol. 2013;27:949-60.

60. Nedelciuc O, Pintilie I, Dranga M, Mihai C, Prelipcean CC. Quality of life in patients with ulcerative colitis. Rev Med Chir Soc Med Nat Iasi. 2012;116:756-60.

61. Kim ES, Cho KB, Park KS, Jang BI, Kim KO, Jeon SW, et al. Predictive factors of impaired quality of life in Korean patients with inactive inflammatory bowel disease: association with functional gastrointestinal disorders and mood disorders. J Clin Gastroenterol. 2013;47:e38-44.

62. Barile JP, Mitchell SA, Thompson WW, Zack MM, Reeve BB, Cella D, et al. Patterns of Chronic Conditions and Their Associations With Behaviors and Quality of Life, 2010. Prev Chronic Dis. 2015;12:E222.

63. Zhou Y, Ren W, Irvine EJ, Yang D. Assessing health-related quality of life in patients with inflammatory bowel disease in Zhejiang, China. J Clin Nurs. 2010;19:79-88.

64. Bernklev T, Jahnsen J, Lygren I, Henriksen M, Vatn M, Moum B. Health-related quality of life in patients with inflammatory bowel disease measured with the short form-36: psychometric assessments and a comparison with general population norms. Inflamm Bowel Dis. 2005;11:909-18.

65. Vollebregt PF, van Bodegraven AA, Markus-de Kwaadsteniet TML, van der Horst D, Felt-Bersma RJF. Impacts of perianal disease and faecal incontinence on quality of life and employment in 1092 patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2018;47:1253-60.

66. Hoivik ML, Moum B, Solberg IC, Cvancarova M, Hoie O, Vatn MH, et al. Health-related quality of life in patients with ulcerative colitis after a 10-year disease course: results from the IBSEN study. Inflamm Bowel Dis. 2012;18:1540-9.

67. Hjortswang H, Jarnerot G, Curman B, Sandberg-Gertzen H, Tysk C, Blomberg B, et al. The influence of demographic and disease-related factors on health-related quality of life in patients with ulcerative colitis. Eur J Gastroenterol Hepatol. 2003;15:1011-20.

68. Romberg-Camps MJ, Bol Y, Dagnelie PC, Hesselink-van de Kruijs MA, Kester AD, Engels LG, et al. Fatigue and health-related quality of life in inflammatory bowel disease:

results from a population-based study in the Netherlands: the IBD-South Limburg cohort. Inflamm Bowel Dis. 2010;16:2137-47.

69. Casellas F, Arenas JI, Baudet JS, Fabregas S, Garcia N, Gelabert J, et al. Impairment of health-related quality of life in patients with inflammatory bowel disease: a Spanish multicenter study. Inflamm Bowel Dis. 2005;11:488-96.

70. McMullan C, Pinkney TD, Jones LL, Magill L, Nepogodiev D, Pathmakanthan S, et al. Adapting to ulcerative colitis to try to live a 'normal' life: a qualitative study of patients' experiences in the Midlands region of England. BMJ Open. 2017;7:e017544.

71. Kim S, Park S, Koh H, Kang Y, Kwon N. Medical staff tend to underestimate the quality of life in children and adolescents with inflammatory bowel disease. Acta Paediatr. 2018. [In press]

72. Tormey LK, Reich J, Chen YS, Singh A, Lipkin-Moore Z, Yu A, et al. Limited Health Literacy Is Associated With Worse Patient-Reported Outcomes in Inflammatory Bowel Disease. Inflamm Bowel Dis. 2018. [In press]

8. SUMMARY

Objectives: Adaptation to ulcerative colitis (UC) is very complex as it has a huge impact in the quality of life of those who suffer with it. In the present study the objective was to determine the differences in quality of life between UC patients and a control group.

Patients and Methods: This study included 30 patients with ulcerative colitis and 30 age and sex-matched control subjects. The diagnosis was based on medical history in addition to clinical, radiological, endoscopic and histological features. Health-related quality of life (HRQoL) was measured by the Short Form-36 (SF-36) questionnaire, a multifunctional, non-disease specific, 36-item health survey. Statistical software MedCalc ver. 11.5.1.0 for Windows (MedCalc Software, Ostend, Belgium) was used for statistical data analysis.

Results: Significant differences between groups were observed in 2 domains, domain role limitations due to physical health and domain general health. The mean value for the self-assessment of quality of life for UC patients was 7 in comparison to the control group which had a mean value of 9. This demonstrated that patients with ulcerative colitis perceived their quality of life as significantly lower than the control patients. Negative correlation was found between UC duration and 3 domains of SF-36 questionnaire: physical functioning (r=-0.519, P=0.003), role limitations due to physical health (r=-0.434, P=0.017) and general health (r=-0.358, P=0.050). There was no significant correlation observed between disease duration and other domains of the SF-36 questionnaire. Quality of life remains similar among patients regardless of their disease activity. There were no significant differences observed in any SF-36 domains among patients with active UC and patients whose disease is currently not active.

Conclusion: Results confirmed the hypothesis that patients with UC have reduced quality of life when compared to healthy individuals.

9. CROATIAN SUMMARY

Naslov: PROCJENA KVALITETE ŽIVOTA U BOLESNIKA S ULCEROZNIM KOLITISOM

Ciljevi: Prilagodba ulceroznom kolitisu (UC) je vrlo složena jer ima veliki utjecaj na kvalitetu života onih koji pate od ove bolesti. U ovome radu cilj je bio utvrditi razlike u kvaliteti života između bolesnika s UC i kontrolne skupine.

Pacijenti i metode: Ova studija obuhvatila je 30 bolesnika s ulceroznim kolitisom i 30 kontrolnih ispitanika, slične dobi i spola. Dijagnoza se temeljila na medicinskoj povijesti uz kliničke, radiološke, endoskopske i histološke značajke. Kvaliteta života povezana sa zdravljem (HRQoL) mjerena je upitnikom SF-36, višenamjenskom, zdravstvenom anketom. Statistički softver MedCalc ver. 11.5.1.0 za Windows (MedCalc Software, Ostend, Belgija) korišten je za statističku analizu podataka.

Rezultati: Značajne razlike među skupinama zabilježene su u 2 domene, domena ograničenja uloga zbog fizičkog zdravlja i domena općeg zdravstvenog stanja. Srednja vrijednost za samoprocjenu kvalitete života za pacijente s UC bila je 7 u usporedbi s kontrolnom skupinom koja je imala srednju vrijednost 9. To je pokazalo da su pacijenti s ulceroznim kolitisom znali da je njihova kvaliteta života znatno niža od kontrole pacijenata. Negativna korelacija je utvrđena između trajanja UC i 3 domene SF-36 upitnika: fizičko funkcioniranje ($r = -0.519$, $P = 0.003$), ograničenja uloga zbog tjelesnog zdravlja ($r = -0.434$, $P = 0.017$) i opće zdravstveno stanje ($r = -0,358$, $P = 0,050$). Nije zabilježena značajna korelacija između trajanja bolesti i ostalih područja SF-36 upitnika. Kvaliteta života ostaje slična među pacijentima bez obzira na njihovu aktivnost bolesti. Nije bilo značajnih razlika u bilo kojoj SF-36 domeni među pacijentima s aktivnim UC i bolesnicima čija je bolest trenutno neaktivna.

Zaključak: Rezultati potvrđuju hipotezu da pacijenti s UC imaju smanjenu kvalitetu života u usporedbi sa zdravim pojedincima.

10. CURRICULUM VITAE

Personal Data:

Name and Surname: Alvaro Gomez Diaz

Date of birth: January 6th 1991 in Las palmas de Gran Canaria (Spain)

Citizenship: Spanish

Address: Calle lepanto 4,2 D (Las palmas)

E-mail: varo_gd91@hotmail.com

Education:

2013-2018 University of Split School of Medicine, Split, Croatia

2010-2013 University of Pecs Medical school, Hungary

2009-2010 Premedical course, Mc Daniel college Budapest, Hungary

1997-2009 Colegio Hispano Ingles de las Palmas de Gran Canaria

Languages:

Spanish (mother tongue)

English (C1) German (A2) Italian (A2) Croatian (A1) Hungarian (A1)