Infliximab for Crohn's Disease Patients with Perianal Fistulas: Better Image, Better Life

Authors' Contribution:
Study Design **A**
Data Collection **B**
Statistical Analysis **C**
Data Interpretation **D**
Manuscript Preparation **E**
Literature Search **F**
Funds Collection **G**

AD **Liwen Hong***
BD **Chen Zhang***
BC **Rong Fan**
BC **Lei Wang**
F **Zhengting Wang**
AF **Tianyu Zhang**
AEF **Jie Zhong**

Department of Gastroenterology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, P.R. China

Corresponding Authors:
Source of support:

* Liwen Hong and Chen Zhang contributed equally to this article
Tianyu Zhang, e-mail: zhty0718@yeah.net, Jie Zhong, e-mail: jimmyzj64@hotmail.com
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Background: Patients with Crohn's disease (CD) experience physical impairments, poor quality of life and negative body image. These factors are exacerbated in CD patients with active perianal fistulas.

Material/Methods: Baseline characteristics were compared in retrospectively enrolled CD patients with and without active perianal fistulas. The relationships between improvements in perianal fistulas and quality of life, body image, and self-esteem were determined. The effects of infliximab treatment on improvement of psychological-social status were assessed in CD patients with active perianal fistulas.

Results: Of the 301 CD patients included in our institution's database. 91 (30.2%) had active perianal fistulas. After adjustment by propensity score matching, CD patients with active perianal fistulas had lower self-esteem and more severe body image dissatisfaction than CD patients without active perianal fistulas (P<0.01 each). Perianal fistula response was closely associated with improvements in quality of life, body image dissatisfaction and self-esteem (P<0.01 each). Patients with perianal fistula treated with infliximab showed a response rate of 68.3%, significantly higher than the rate in patients with perianal fistula not treated with infliximab (P=0.005). Furthermore, improvements of life quality, body image and self-esteem were significantly greater in patients with perianal fistula who were than were not treated with infliximab (P<0.05 each).

Conclusions: CD patients with active perianal fistulas experience body image dissatisfaction, low self-esteem and poor quality of life. Treatment of these patients with infliximab could improve their body image, self-esteem and quality of life.

MeSH Keywords: Body Image • Crohn Disease • Fistula • Quality of Life

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Background

Crohn's disease (CD), a subtype of inflammatory bowel disease, is a chronic and relapsing disease affecting the entire gastrointestinal tract with systemic manifestations. The etiology of CD is incompletely understood, although multiple factors have been reported to contribute to the onset of disease. Symptoms of CD can be severe, including abdominal pain, diarrhea, gastrointestinal bleeding, abdominal distension, weight loss, malnutrition and several extra-intestinal manifestations and complications [1]. One of the most frequent complications of CD is perianal fistula (PF), which is strongly associated with increased rates of hospitalization, intestinal resection, and disease recurrence [2], making PF a predictor of poor long-term outcomes in CD patients.

Advances in treatment, including the anti-TNF-α antibody Infliximab (IFX), have led to profound improvements in CD treatment strategies. IFX has been shown to promote mucosal healing and long-term maintenance of remission. A multicenter, randomized trial found that IFX induction therapy was effective in treating CD patients with PF [3], and the ACCENT II maintenance trial showed that IFX 5 mg/kg body weight every 8 weeks maintained disease response for 54 weeks in 36% of patients with fistulizing CD [4].

In addition to physical impairments, CD patients experience reduced health-related quality of life (QoL) [5,6], a negative body image (BI) and lower self-esteem (SE) [7–9], which negatively affect their social-psychological well-being. Few studies, however, have assessed the social and psychological effects experienced by CD patients with PF. Moreover, the effects of IFX on the social-psychological status of CD patients with PF have not been determined. The present study therefore assessed whether the presence of active PF (APF) could directly influence QoL, BI and SE of CD patients, and whether IFX could ameliorate their social-psychological impairments.

Material and Methods

Patient enrollment

This study was approved by the ethics committee of Shanghai Ruijin Hospital. Information about treatment-naïve patients diagnosed with CD between September 2016 and August 2018 by the gastroenterology service of Shanghai Ruijin Hospital were retrospectively collected from the hospital's CD patient database. The diagnosis of CD was based on patients' clinical symptoms, serologic tests, endoscopic examinations and pathologic results. The data retrieved at the time of CD diagnosis included age at diagnosis, gender, level of education, marital status, level of family income, body mass index (BMI), disease type according to the Montreal classification, and

Harvey-Bradshaw Index (HBI). Data retrieved for patients with APF also included fistula type and severity. All of the enrolled patients had signed written informed consent forms. Patients aged <18 or >60 years, pregnant and lactating women, patients who also had other chronic diseases and those with incomplete baseline data were excluded. All data were stored and processed anonymously.

Short-Form of Inflammatory Bowel Disease Questionnaire (SIBDQ)

QoL was assessed using the Chinese version of the SIBDQ. The SIBDQ consists of ten questions about four dimensions of IBD: bowel (defecation frequency, abdominal pain), systemic discomfort (fatigue), social status (impact of disease on daily life) and emotional issues (concerns about surgery, anxiety). Each question was scored on a seven-point scale (1 to 7), with higher scores indicating better QoL [10].

Body Image Scale (BIS)

The BIS questionnaire consists of 9 items measuring behavioral, affective, and cognitive dimensions of BI and has been validated for CD patients [7]. Each item is rated on a 4-point Likert scale (0 to 3). Higher scores represent more body image-related distress or body image concerns.

Rosenberg Self-Esteem Scale (RSE)

General self-esteem (SE) was assessed using the 10-item RSE questionnaire. Each item on the RSE is rated on a four-point Likert scale (1 to 4), with higher scores indicating higher levels of SE [11].

Perianal Crohn's Disease Activity Index (PCDAI)

The PCDAI is a self-reported questionnaire concerning five clinical dimensions: discharge; activity restriction; sexual activity restriction; perianal disease type and degree of PF induration. Each dimension is scored from 0 to 5 points, with higher scores indicating more severe disease [12].

Data collection

CD patients with at least one draining PF were defined as having an APF. Treatment efficacy was assessed by clinical evaluation at each follow-up visit according to items on the HBI and PCDAI. Perianal fistula response (PFR) was defined as a ≥50% reduction from baseline in the number of draining PFs, as determined by gentle compression. All CD patients with APF were followed up for 6–12 months after diagnosis. Improvement was defined as a higher SIBDQ, lower BIS, higher RSE and lower PCDAI relative to baseline.

Matching

Because BI has been associated with gender, age, BMI and support from peers or family [13,14], positive SE has been associated with higher education level and male gender [15,16], and reduced QoL has been associated with disease activity and phenotype [17], CD patients with and without APF were subjected to propensity score matching (PSM). Propensity scores were based on baseline variables, including age, gender, educational level, marital status, family income level, BMI level, disease classification and HBI index. Nearest neighbor matching was performed in a 1: 1 ratio without replacement, and caliber width was set at a standard deviation (SD) of 0.2.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences ver. 22.0 (SPSS, Chicago, IL). Before PSM matching, normally distributed continuous data were presented as means with SDs and were compared using independent sample t tests. Qualitative data were presented as frequency with percentage and compared using chi-square or Fisher's exact test. After PSM, normally distributed continuous data were compared using paired sample t tests. Paired sample t tests were also used to compare questionnaire scores before and after treatment of patients with APF. P-values <0.05 were considered statistically significant.

Results

Patients' demographic and clinical characteristics

The flowchart of this study is shown in Figure 1. Data on 322 patients with CD were retrieved from the hospital database. Twenty-one of these patients were excluded, including 14 with incomplete baseline data, six with concomitant disease, and one who was pregnant. Of the 301 patients included in the primary analysis, 91 (30.2%) had APF. Table 1 shows the baseline clinical characteristics of all included patients. Of the 91 patients with APF, three underwent surgery for severe perianal complications and two were lost to follow-up. Finally, 86 CD patients with APF were enrolled.

To analyze the impact of APF on social-psychological status, patients with CD were divided into two groups, those with and without APF. Table 2 shows the demographic characteristics of these patients before and after PSM matching. Before PSM matching, there were no significant between-group differences in gender, educational level, marital status, income level, disease location and disease behavior according to the Montreal criteria (P>0.05 each). However, median age was lower in patients with than without APF (33.7 years *vs.* 35.3 years,
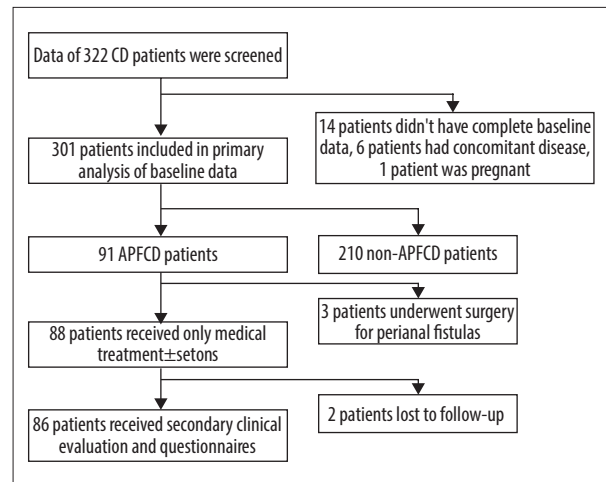

Figure 1. Flowchart of study patients.

P=0.041). In addition, BMI was significantly lower (P=0.026) and HBI score significantly higher (P<0.001) in patients with than without APF. Moreover, assessments of psychological-social status parameters showed that SIBDQ (P=0.016), RSE (P<0.001) and BIS (P<0.001) scores were significantly higher in CD patients with than without APF.

Because psychological-social parameters could be influenced by multiple factors, PSM of the two groups was performed to minimize the selection bias caused by psychological-social parameters (Table 2, matched cohort). Of all 91 patients with APF, 82 (90.1%) could be matched successfully to patient without APF according to gender, age, educational level, marital status, income level, BMI, disease location, disease behavior and HBI. Following PSM matching, there were no significant differences in baseline characteristics and SIBDQ scores between CD patients with and without APF. However, RSE scores were significantly lower (P<0.001) and BIS scores significantly higher (P<0.001) in CD patients with than without APF, indicating that patients with APF had a lower level of self-esteem and greater body image dissatisfaction.

PFR and psychological-social status in CD patients with APF

The clinical features of PF type and the concomitant treatment of the 86 CD patients with APF are listed in Table 3. Of these 86 patients, 45 (52.3%) achieved PFR, whereas 41 (47.7%) had persistent APF. However, the proportion of patients with a single PF was significantly higher in the PFR than in the non-PFR group (P=0.046). Moreover, the proportion of patients treated with IFX was significantly higher in the PFR than in the non-PFR group (P=0.005). A comparison of the changes in scores of the four questionnaires before and after treatment showed that improvements in PCDAI (P<0.01), SIBDQ (P=0.003), RSE (P<0.001) and BIS (P<0.01) scores were significantly greater in the PFR than in the non-PFR group (Table 3, Figure 2).

Table 1. Baseline demographic and clinical characteristics of CD patients.

Clinical features	CD patients (n=301)	
Age, y	34.8±10.3	
Female, n (%)	204	(67.8)
Education, n (%)		
≤9 years	62	(20.6)
10–12 years	111	(36.9)
≥13 years	128	(42.5)
Marital status, n (%)		
Single	119	(39.5)
Married/cohabitant	182	(60.5)
Family Income, n (%)		
Low	41	(13.6)
Middle	200	(66.4)
High	60	(19.9)
BMI, n (%)		
<18.5 kg/m^2	77	(25.6)
18.5–24.9 kg/m^2	209	(69.4)
>25 kg/m^2	15	(5.0)

Clinical features	CD patients (n=301)	
Disease location, n (%)		
L1 (ileal)	78	(25.9)
L2 (colonic)	82	(27.2)
L3 (ileocolonic)	141	(46.8)
Disease behavior, n (%)		
B1 (non-stricturing, non-penetrating)	228	(75.7)
B2 (stricturing) and/or B3 (penetrating)	73	(24.3)
Patients with APF, n (%)	91	(30.2)
HBI	5.3±4.0	
Social-psychological index		
SIBDQ	53.3±7.5	
RSE	26.8±5.9	
BIS	8.1±3.3	

IFX improvement of psychological-social status in CD patients with APF

To further analyze the role of IFX treatment in improving social-psychological status in CD patients with APF, we compared the PFR rate and the improvements in PCDAI, SIBDQ, RSE and BIS scores between the IFX and non-IFX groups (Table 4). In the IFX group, the PFR rate was 68.3%, which was significantly higher than in the non-IFX group (P=0.005). Furthermore, improvements in PCDAI (P= 0.003), SIBDQ (P=0.015), RSE (P=0.011) and BIS (P=0.020) scores were significantly greater in the IFX than in the non-IFX group (Table 4, Figure 3).

Discussion

Body image dissatisfaction (BID) is quite common in CD patients, with recent studies reporting BID in 21–87% of these patients [7,14,18]. Moreover, some IBD patients may be at risk of low SE [8], and the combination of increased BID and low SE has been associated with reduced QoL [7,19]. To our knowledge, however, BID and SE had never been fully evaluated in CD patients with APF, nor had their improvements in response to treatment.

The present study found that CD patients with APF were younger and had lower BMI and more severe disease activity than

CD patients without APF. Because BID, SE and QoL are associated with many social-clinical parameters, we performed PSM to exclude these possible interfering factors. Analysis following PSM showed that BID was higher and SE and QoL lower in CD patients with than without APF. Thus, medications that could induce PFR may improve BID, SE and QoL scores in CD patients with APF. Indeed, we found that PFR was strongly associated with improvements in BID, SE and QoL. Because IFX has been shown to induce PFR in CD patients with APF, it may also improve BID, SE and QoL in these patients.

IFX, the first biologic anti-TNFα agent approved for CD patients in China, has been shown effective in inducing deep remission of PF, resulting in clinical improvement [20]. Our study found that IFX treatment resulted in a PFR rate of 68.3% in CD patients with APF, a rate higher than that previously reported [4]. The improvement in PFR rate may be due to the synergistic effects of IFX with other concomitant medications. Induction treatment with IFX resulted in a higher level of SIBDQ and improved QoL. Similar, IFX has been shown to improve QoL in CD patients [21–23]. Moreover, our study revealed that IFX could significantly improve BI and SE in CD patients with APF. To our knowledge, this study is the first to show that IFX could improve overall social-psychological status in CD patients with APF.

This study had several limitations. First, although patients were compared after PSM, this study was limited by its retrospective design and the limited number of patients. Long-term, multi-center, prospective randomized controlled trials are needed to further determine the effect of IFX on improving BID, SE and

Table 2. Baseline demographic and clinical characteristics of CD patients with and without APF.

Patient characteristics	Total cohort			Propensity Score Matched cohort		
	With APF (n=91)	Without APF (n=210)	P value	With APF (n=82)	Without APF (n=82)	P value
Age, y	33.7±11.3	35.3±9.8	0.041	33.8±10.8	32.8±10.9	0.630
Female, n (%)	61 (67.0)	143 (68.1)	0.857	58 (70.7)	52 (63.4%)	0.391
Education level, n (%)			0.067			0.513
≤9 years	19 (20.9)	43 (20.4)		22 (26.8)	29 (35.4%)	
10–12 years	43 (47.3)	68 (32.4)		45 (54.9)	34 (41.5%)	
≥13 years	29 (31.9)	99 (47.1)		15 (18.3)	19 (23.2%)	
Marital status, n (%)			0.438			0.635
Single	39 (42.9)	80 (38.1)		34 (41.5)	38 (46.3%)	
Married/cohabitant	52 (57.1)	130 (61.9)		48 (58.5)	44 (53.7%)	
Income level, n (%)			0.336			0.307
Low	14 (15.4)	27 (12.9)		12 (14.6)	11 (13.4%)	
Mediate	55 (60.4)	145 (69.0)		50 (61.0)	59 (72.0%)	
High	22 (24.2)	38 (18.1)		20 (24.4)	12 (14.6%)	
BMI, n (%)			0.026			0.181
<18.5 kg/m^2	30 (33.0)	47 (22.4)		25 (30.5)	19 (23.2%)	
18.5–24.9 kg/m^2	59 (64.8)	150 (71.4)		55 (67.1)	58 (70.7%)	
>25 kg/m^2	2 (2.2)	13 (6.2)		2 (2.4)	5 (6.1%)	
Disease location, n (%)			0.326			0.963
L1 (ileal)	19 (20.9)	59 (28.1)		18 (22.0)	20 (24.4%)	
L2 (colonic)	27 (29.7)	55 (26.2)		24 (29.3)	20 (24.4%)	
L3 (ileocolonic)	45 (49.5)	96 (45.7)		40 (48.8)	42 (51.2%)	
Disease behavior, n (%)			0.251			0.857
B1 (non-stricturing, non-penetrating)	65 (71.4)	163 (77.6)		61 (74.4)	62 (75.6%)	
B2 (stricturing) and/or B3 (penetrating)	26 (28.6)	47 (22.4)		21 (25.6)	20 (24.4%)	
HBI	6.0±3.9	5.0±4.0	<0.001	5.8±4.0	5.9±4.3	0.971
Social-psychological index						
SIBDQ	51.7±8.0	54.0±7.1	0.016	52.0±7.7	53.4±7.6	0.252
RSE	23.9±5.7	28.0±5.5	<0.001	23.6±5.7	27.6±5.5	<0.001
BIS	9.9±2.6	7.3±3.3	<0.001	10.0±2.5	8.1±3.0	<0.001

Table 3. Relationship between PF remission and improvement of social-psychological status.

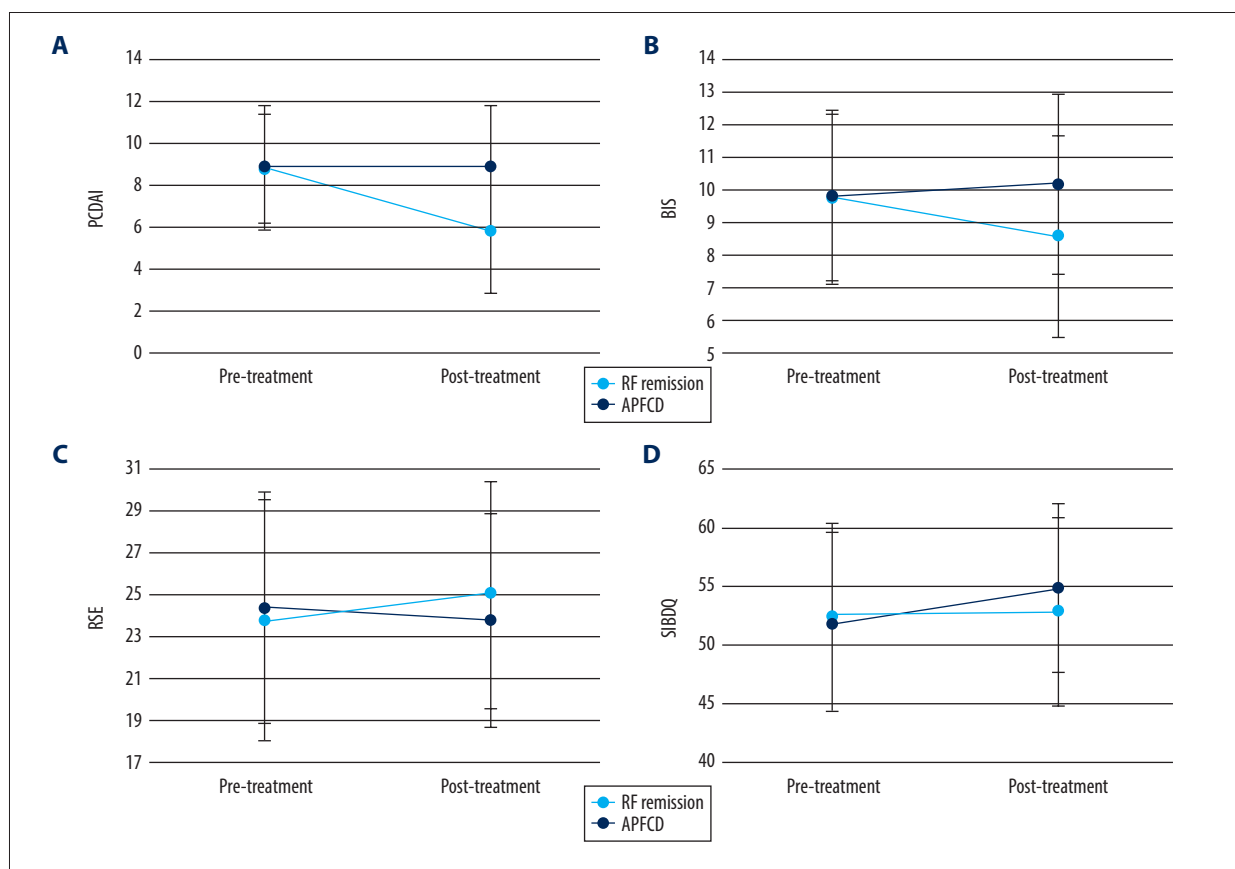|	Patients with PF remission n=45	Patients with persistent APF n=41	P value
PF type, n (%)			0.046
Simple perianal fistula	25 (55.6)	14 (34.1)	
Complex perianal fistulas	20 (44.4)	27 (65.9)	
Treatment, n (%)			0.005
With IFX	28 (62.2)	13 (31.7)	
Without IFX	17 (37.8)	28 (68.3)	
Improvement of PCDAI	3.0±1.8	−0.1±1.4	<0.010
Improvement of SIBDQ	2.7±3.8	0.4±3.0	0.003
Improvement of RSE	1.2±2.8	−0.6±2.2	0.001
Improvement of BIS	1.2±2.4	−0.4±1.8	<0.010

Figure 2. Improvements in PCDAI (**A**), BIS (**B**), RSE (**C**) and SIBDQ (**D**) in CD patients with PF remission and persistent APF.
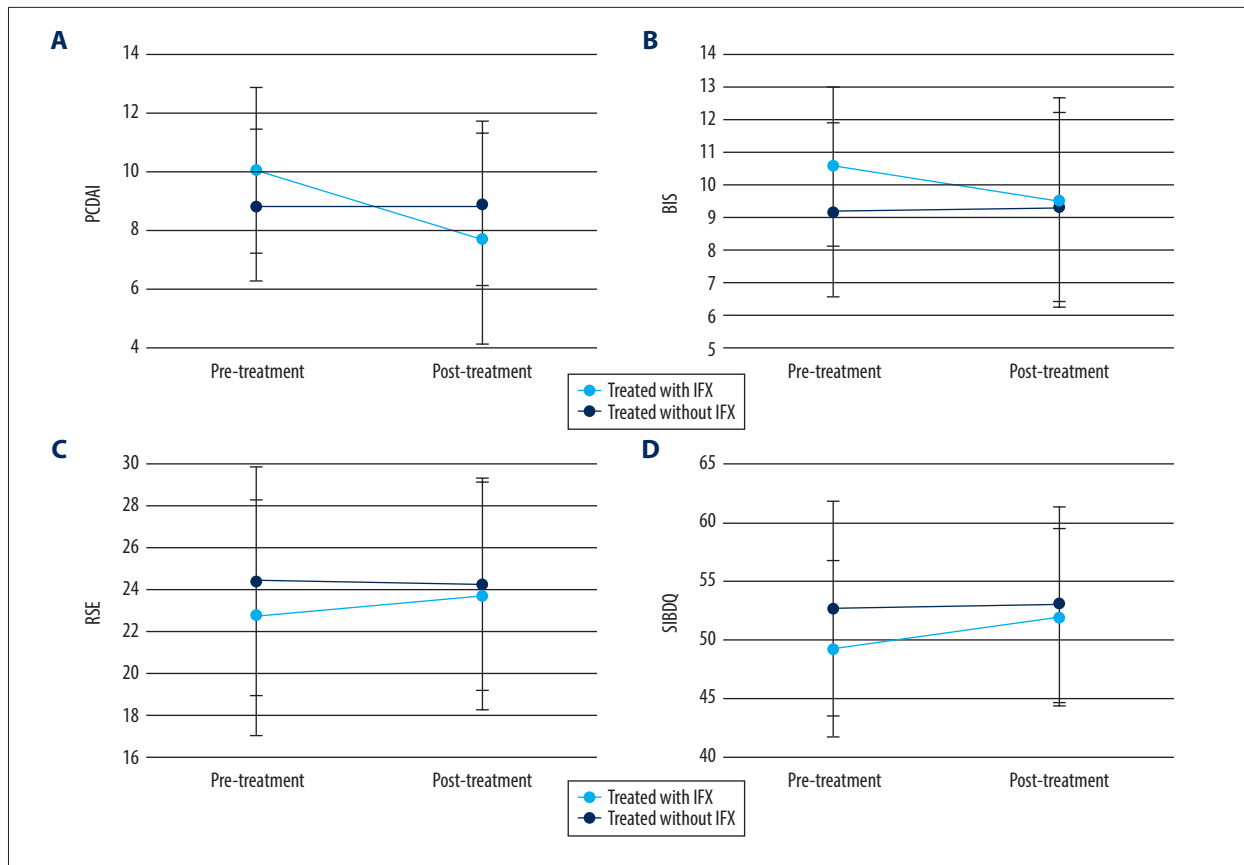
Figure 3. Improvements in PCDAI (**A**), BIS (**B**), RSE (**C**) and SIBDQ (**D**) in CD patients treated with and without IFX.

Table 4. The role of IFX in PF remission and improvement of social-psychological status.

	Patients treated with IFX n=41	Patients treated without IFX n=45	P value
PF remission, n(%)	28 (68.3)	17 (37.8)	0.005
Improvement of PCDAI	2.3±2.4	0.9±1.9	0.003
Improvement of SIBDQ	2.6±3.9	0.7±3.2	0.015
Improvement of RSE	1.1±2.8	−0.4±2.5	0.011
Improvement of BIS	1.0±2.1	−0.1±2.1	0.020

QoL in CD patients with APF. Second, we did not stratify patients by time of evaluation, IFX dosing strategy, or treatment with concomitant medications.

Conclusions

In conclusion, CD patients with APF experience greater BID, lower SE and poorer QoL than CD patients without APF. The presence of APF seriously affected the overall physio-psycho-social health of CD patients. IFX was shown to improve PF, thereby improving patient BID, SE and QoL.

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