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Original Article

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# Comparison of Costs and Quality of Life in Ulcerative Colitis Patients with an Ileal Pouch–Anal Anastomosis, Ileostomy and Anti-TNFα Therapy

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## Abstract

**Background and Aims:** More data are warranted on the economic impact of different treatment strategies in ulcerative colitis (UC) patients. We compared the costs and quality of life of UC patients with a pouch reconstruction, an ileostomy or anti-tumour necrosis factor α (TNFα) therapy.

**Methods:** UC patients filled out 3-monthly questionnaires for 2 years. Differences in 3-monthly healthcare costs, productivity costs and patient costs were tested using mixed model analysis. Quality of life was assessed employing the ) and the inflammatory bowel disease questionnaire (IBDQ).

**Results:** Out of 915 UC patients, 81 (9%) had a pouch and 48 (5%) an ileostomy, and 34 (4%) were on anti-TNFα therapy. Anti-TNFα-treated patients reported high UC related-healthcare costs

per 3 months (€5350). Medication use accounted for 92% of healthcare costs. UC-attributable healthcare costs were 3-fold higher in ileostomy patients compared with pouch patients (€1581 versus €407; $p < 0.01$). Main cost drivers in ileostomy patients were healthcare costs and ileostomy supplies (2 and 23% of healthcare costs, respectively). In pouch patients, the main cost driver was hospitalization, accounting for 50% of healthcare costs. Productivity loss did not differ between pouch and ileostomy patients (€483 versus €377; $p < 0.23$), but was significantly higher in anti-TNFα-treated patients (€1085). No difference was found in IBDQ scores, but pouch patients were found to have higher quality-adjusted life years than ileostomy patients and anti-TNFα-treated patients (0.90 [interquartile range 0.78–1.00] versus 0.84 [0.78–1.00] and 0.84 [0.69–1.00], respectively; $p < 0.01$).
**Conclusion:** Patients receiving anti-TNFα therapy reported the highest healthcare cost, in which medication use was the major cost driver. Ileostomy patients were three times more expensive than pouch patients due to frequent hospitalization and ileostomy supplies.

## 1. Introduction

The management of ulcerative colitis (UC) has changed dramatically over the past 10 years, with an increasing role of anti-TNFα drugs in patients failing conservative therapy.[1] However, anti-TNFα therapy is expensive and accounts for one-third of UC-related healthcare costs.[2]

A restorative proctocolectomy with construction of an ileoanal pouch–anal anastomosis (pouch) is an alternative treatment option. Pouch surgery preserves body image and restores the conservative route of defaecation.[3] However, the construction of a pouch is a difficult surgical procedure and complications are common, such as the occurrence of pouchitis,[4–7] and decreased fecundity in young women.[8] Recently, a significant reduction of complications after pouch surgery has been reported and overall success rates of 96.3% after 5 years, 92.4% after 10 years and 92.1% after 20 years have been described.[9]

In the emergency setting or in case of contraindications for pouch surgery, such as an impaired sphincter function, significant comorbidities or an unclear diagnosis (inflammatory bowel disease [IBD]-unclassified), the surgical procedure of choice is a colectomy with an end-ileostomy and a closed rectal stump.[3] A number of studies have shown that this procedure is safe in the emergency setting with a post-operative complication rate varying from 23 to 33%.[10,11] In the absence of contraindications, pouch reconstruction may be considered over time in these cases as well.

To date, no studies comparing long-term outcomes of medically versus surgically treated patients have been published. In the light of the escalating costs of healthcare, more data on the economic impact of different treatment strategies are warranted in UC patients failing conservative treatment. We aimed to study the costs and quality of life of UC patients with a pouch, an ileostomy or anti-TNFα treatment using a cross-sectional, prospectively followed cohort.[2]

## 2. Methods

### 2.1. Study design

In 2010 we initiated the Costs Of Inflammatory Bowel Disease (COIN) study in The Netherlands in order to evaluate the total costs of IBD. We have published the cohort organization and results on the internal validity of our cohort in detail elsewhere.[2,12] In summary, between October 2010 and October 2011 we invited by letter all identified IBD patients aged 18 years or older from seven university hospitals and seven general hospitals to participate in the COIN study. Identification was based on diagnosis–treatment combinations. We developed a secure web-based questionnaire to obtain longitudinal data on costs and quality of life. All patients were followed up for 2 years at 3-month intervals. The web-based questionnaires contained questions on demographic and clinical characteristics, as well as costs and quality of life. Demographic characteristics included sex, age, age at diagnosis, education level, work status and smoking status. Clinical characteristics included subtype of IBD, disease duration and localization, penetrating disease course and self-reported disease activity.

### 2.2. Patient population

For the current analysis we compared three groups of UC patients. The first group consisted of UC patients who had had pouch surgery before the start of the study. The second group were patients who reported having had a colectomy with formation of an ileostomy before the start of the study. The third group consisted of UC patients on infliximab or adalimumab therapy (anti-TNFα therapy).

### 2.3. UC-related costs

We analysed UC-related costs from a societal perspective, including three main cost categories, as suggested by Drummond et al.,[13] outlined in Table 1. Healthcare costs were calculated by multiplying self-reported units of UC-related resource utilization by their unit prices (see Supplementary Table S1). To assess productivity losses, we used self-reported sick leave of employed patients from paid work. The number of sick leave days per week was limited to a maximum of 5. Hours of sick leave were valued using age- and sex-specific unit prices as presented in Supplementary Table S1. Patient costs, including deductibles for healthcare insurances, over-the-counter drugs and travel costs, were calculated according to patient specifications. All costs are expressed in euros for the year 2011. Discounting was not applied due to the short time period considered (2 years).

### 2.4. Quality of life

To assess disease-specific quality of life, we used the Dutch version of the Inflammatory Bowel Disease Questionnaire (IBDQ).[14] In addition, the EuroQol group EQ-5D-3L questionnaire was employed as a generic tool for quality-of-life measurement.[15] The IBDQ consists of 32 items grouped into four dimensions: bowel symptoms, systemic symptoms, emotional function and social function. The answers are rated on a graded response range from 'worst' (1) to 'best' (7) and a possible total score with a minimum of 32 (i.e. 'worst' score) to a maximum of 224 (i.e. 'best' score). The EQ-5D-3L consists of a descriptive system and comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has three levels: (1) no problems; (2) some problems; and

(3) extreme problems. EQ-5D health states, defined by the EQ-5D descriptive system, are converted into a weighted health state index (utility), the so-called quality-adjusted life year (QALY) using the Dutch EQ-5D tariff elicited from a Dutch general population sample.[16] The QALY values obtained in this way lie on a scale on which full health has a value of 1 and dead a value of 0.

### 2.5. Ethical considerations

The study was centrally approved by the ethics committee of the University Medical Centre Utrecht.

### 2.6. Statistical analysis

Data analysis was performed using SPSS version 18.0 (Chicago, IL, USA). Descriptive statistics were used to characterize the three study groups. Means and medians were reported with a standard deviation (SD) and an interquartile range (IQR), respectively. Differences amongst baseline characteristics were assessed by one-way ANOVA for continuous variables and the $\chi^2$ test for dichotomous variables. To account for missing data, we used a generalized mixed model to calculate the 3-month costs and quality of life. Despite the skewed nature of cost data, we reported mean costs (with 95% confidence intervals), as overall total costs then can be calculated. Quality-of-life scores were presented as median and IQR.

## 3. Results

Figure 1 shows the study flowchart. Of the 915 UC patients included in the COIN study, 163 patients met the inclusion criteria, including 81 (9%) with a pouch, 48 (5%) with an ileostomy and 34 (4%) on anti-TNFα therapy. In total 51/81 (63%) pouch patients, 27/48 (56%) ileostomy patients and 25/34 (74%) patients receiving TNFα therapy filled out the 2-year follow-up questionnaire. The number of responders per 3-month intercept is provided in Supplementary Table S2.

Table 2 shows the baseline characteristics of the three study groups. Patients with an ileostomy were older than patients with a pouch or patients on anti-TNFα ($p < 0.07$). Patients on anti-TNFα therapy were more likely to be female compared with stoma and pouch patients, although this did not reach significance ($p = 0.48$). The median time since surgery was not different between pouch and ileostomy patients ($p = 0.77$). Clinical disease activity was reported by 35% of the patients on anti-TNFα therapy. The mean treatment duration of anti-TNFα therapy was 2 years in patients treated with infliximab and 1 year in those treated with adalimumab ($p = 0.77$).

### 3.1. UC-related healthcare use and associated costs

Table 3 presents the mean 3-month resource use within healthcare. Anti-TNFα patients were more likely to visit the gastroenterologist ($p < 0.01$), a specialized nurse ($p < 0.01$), an internist ($p < 0.01$) and a rheumatologist ($p < 0.01$) compared with pouch and ileostomy patients. Ileostomy patients visited a specialized nurse and surgeon more often compared with pouch patients ($p = 0.01$). Colonoscopies and ileoscopies were more often performed in anti-TNFα-treated patients compared with pouch and ileostomy patients. 'No medication use' was encountered significantly more often in ileostomy patients compared with pouch patients ($p < 0.01$). Ileostomy patients were more often hospitalized compared with patients in the pouch group ($p < 0.01$). In the anti-TNFα group, 80% received infliximab and 20% received adalimumab ($p < 0.01$). Of all anti-TNFα-treated patients, 42% received combination therapy with

**Table 1.** UC-related cost categories and quality-of-life questionnaires used.

| Healthcare | Productivity | Patient | Quality of life |
|---|---|---|---|
| Surgery<br>Hospitalization<br>Outpatient clinic<br>Medication use<br>Diagnostics Procedures<br>Ileostomy supplies | Absenteeism (number of sick leave days from paid work) | Out-of-pocket costs (e.g. travel costs, deductibles for healthcare insurance, over-the-counter drug use) | Disease-specific:<br>Inflammatory Bowel Disease Questionnaire<br>Generic:<br>Euroqol Group EQ-5D-3L questionnaire |

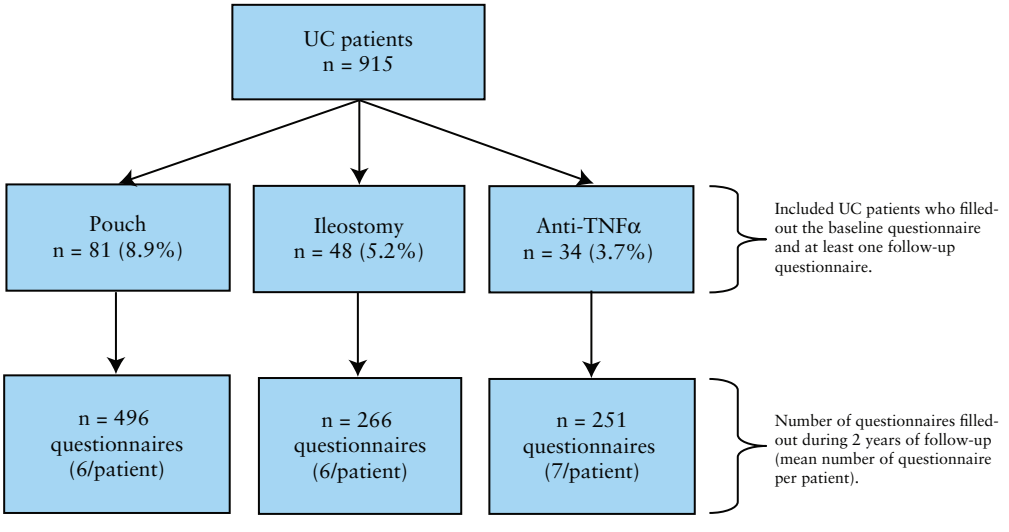


**Figure 1.** Study flowchart.

**Table 2**. Baseline characteristics of UC patients with a pouch, ileostomy versus anti-TNFα patients.

| Characteristic | Pouch ($n$ = 81) | Ileostomy ($n$ = 48) | Anti-TNFα ($n$ = 34) | $p$-value |
|---|---|---|---|---|
| Demographic characteristics | | | | |
| Female gender (%) | 36 (44.4) | 21 (43.8) | 19 (55.9) | 0.48 |
| Age, years (SD) | 46.7 (12.1) | 53.4 (11.6) | 45.4 (10.8) | 0.07 |
| Smoking (%) | | | | 0.61 |
| Current | 7 (8.6) | 1 (2.1) | 2 (5.9) | |
| Never | 49 (60.5) | 30 (62.5) | 17 (50.0) | |
| Ex-smoker | 25 (30.9) | 17 (35.4) | 15 (44.1) | |
| Weight, kg (SD) | 74 (8) | 75 (10) | 74 (10) | 0.58 |
| Employed (%), 18–64 years | 44 (71.0) | 17 (56.7) | 19 (67.9) | 0.39 |
| Disabled (%), 18–64 years | | | | |
| Clinical characteristics | | | | |
| Disease duration (years), median (IQR) | 15 (8.9) | 18 (11.3) | 12.6 (7.8) | 0.10 |
| Self-reported disease activity (%) | n/a | n/a | 12 (35.3) | n/a |
| Bowel complaints | 14 (17.3) | 6 (12.5) | n/a | 0.47* |
| Time since surgery (years), median (IQR) | 12 (3–20) | 11 (2–22) | n/a | 0.63* |
| IBDQ total, mean (SD) | 187 (172–198) | 181 (147–200) | 177 (148–194) | 0.17 |
| QALY, mean (SD) | 0.90 (0.78–1.00) | 0.84 (0.65–1.00) | 0.84 (0.69–1.00) | 0.38 |
| Treatment-related characteristics | | | | |
| Abdominal surgery in the past | n/a | n/a | 2 (5.9) | n/a |
| Medication use in the past (%) | | | | |
| Corticosteroids | 69 (85.2) | 41 (85.4) | 29 (85.3) | |
| Immunomodulators | 40 (49.4) | 19 (39.6) | 27 (79.4) | <0.01 |
| Treatment duration | | | | |
| Infliximab | n/a | n/a | 2.0 (0.7–2.9) | 0.77** |
| Adalimumab | n/a | n/a | 1.1 (0.3–1.9) | |

SD, standard deviation; IQR, interquartile range; IBDQ, inflammatory bowel disease questionnaire; QALY, quality-adjusted life years; n/a, not applicable.
*Pouch versus ileostomy.
**Infliximab versus adalimumab.

immunomodulators. Additional data on healthcare use is presented in Supplementary Tables S3–S5.

Figure 2 depicts the mean 3-monthly healthcare costs per patient. The mean 3-monthly healthcare costs of anti-TNFα patients were €5350, which was significantly higher compared with pouch and ileostomy patients ($p$ < 0.01). Medication use was the main cost driver, accounting for 92% of the healthcare costs. Healthcare costs of ileostomy patients were at least 3-fold higher compared with those of pouch patients (€1581 versus €407; $p$ < 0.01). Hospitalization was the main cost driver in pouch patients (50% of total healthcare costs), followed by medication use, accounting for 23% of healthcare costs. The main cost drivers in ileostomy patients were ileostomy supplies (62%) and hospitalization (23%). More information regarding healthcare costs is presented in Supplementary Tables S3–S5.

### 3.2. Productivity losses and patient costs

Productivity losses due to sick leave from paid work were higher in anti-TNFα-treated patients than in pouch and ileostomy patients (€1085 versus €483 and €377; $p$ < 0.01) Figure 3. Detailed data on sick leave are presented in Supplementary Table S6. Patient costs per 3 months were €42 in pouch patients, €51 in the ileostomy group and €61 in the anti-TNFα group ($p$ = 0.06). According to patient specifications, most expenditures were due to co-payments for medical costs not covered by healthcare insurance, vitamins and other over-the-counter drugs (e.g. anti-diarrhoeal drugs, psyllium fibre) and travel costs.

### 3.3. Quality of life

We found no difference between the median (IQR) IBDQ score in pouch, ileostomy and anti-TNFα-treated patients: 183 (156–198), 181 (165–199) and 181 (159–199), respectively ($p$ = 0.27). However, as presented in Figure 4A and Table S7A, patients with a pouch had lower IBDQ subscores related to bowel symptoms compared with patients in the ileostomy and anti-TNFα groups ($p \leq 0.01$).

Employing the EQ-5D index, QALYs were calculated for the three patient groups. Pouch patients were found to have a significant higher median (IQR) QALY (0.90 [0.78–1.00]) compared with ileostomy patients (0.84 [0.78–1.00]) and anti-TNFα-treated patients (0.84 [0.69–1.00]) ($p \leq 0.01$). Figure 4B and Table S7B show the five dimensions of the EQ-5D-3L. Patients with an ileostomy were found to have more mobility-related problems ($p \leq 0.01$), while anti-TNFα-treated patients had higher pain and discomfort scores compared with the other groups ($p \leq 0.01$).

## 4. Discussion

Before the introduction of anti-TNFα drugs, healthcare costs for UC patients who had previously undergone proctocolectomy were comparable with those for patients on maintenance medical therapy.[17] We expected the introduction of anti-TNFα therapy for induction and maintenance of remission in UC to have profoundly influenced the balance of healthcare costs and quality of life in these treatment groups.

In this unique representative cohort used to document the cost profiles of subgroups of UC patients, we confirmed that the average 3-monthly healthcare costs in UC patients treated with anti-TNFα therapy were indeed substantively higher than in patients in whom a colectomy was performed. In addition, healthcare costs for ileostomy patients were 3-fold higher than the costs for pouch patients, mainly due to hospitalization and costs of ileostomy supplies.

**Table 3.** Mean healthcare use per 3 months (based on all questionnaires filled out during 2 years of follow-up) in UC patients with a pouch, ileostomy or anti-TNFα therapy.

| | Pouch ($n$ = 496) (%) | Ileostomy ($n$ = 266) (%) | Anti-TNFα ($n$ = 251) (%) | $p$-value |
|---|---|---|---|---|
| Outpatient clinic | | | | |
| Gastroenterologist | 134 (27.0) | 81 (30.5) | 116 (46.2) | <0.01 |
| Specialized nurse | 53 (10.7) | 77 (28.9) | 92 (36.7) | <0.01 |
| Internist | 3 (0.6) | 13 (4.9) | 17 (6.8) | <0.01 |
| Dietician | 13 (2.6) | 16 (6.0) | 11 (4.4) | 0.06 |
| Surgeon | 20 (4.0) | 27 (10.2) | 2 (0.8) | <0.01 |
| Rheumatologist | 3 (0.6) | 10 (3.8) | 12 (4.8) | <0.01 |
| Dermatologist | 4 (0.8) | 2 (0.8) | 7 (2.8) | 0.05 |
| Psychiatrist | 2 (0.4) | 3 (1.1) | – | 0.17 |
| Occupational physician | 3 (0.6) | 4 (1.5) | 6 (2.4) | 0.12 |
| Emergency room | 14 (2.8) | 14 (5.3) | 4 (1.6) | 0.05 |
| General practitioner during daytime | 26 (5.2) | 16 (6.0) | 17 (6.8) | 0.69 |
| General practitioner (during night/weekend) | 15 (3.0) | 15 (5.6) | 12 (4.8) | 0.19 |
| Diagnostics procedures | | | | |
| Laboratory | 31 (6.2) | 20 (7.5) | 38 (15.1) | <0.01 |
| Colonoscopy | 11 (2.2) | 7 (2.6) | 28 (11.2) | <0.01 |
| MRI scan | 2 (0.4) | 2 (0.8) | 2 (0.8) | 0.74 |
| CT scan | 3 (0.6) | 3 (1.1) | – | 0.25 |
| Abdominal X-ray | 4 (0.8) | 2 (0.8) | 2 (0.8) | 0.99 |
| Ultrasonography | 4 (0.8) | 2 (0.8) | 4 1.6) | 0.53 |
| DXA scan | 7 (1.4) | 3 (1.1) | 4 (1.6) | 0.900 |
| Medication use | | | | |
| None | 302 (61.0) | 148 (70.2) | n/a | n/a |
| Adalimumab | 5 (1.0) | 4 (1.5) | 49 (20.0) | n/a |
| Infliximab | 3 (0.6) | - | 204 (80.0) | n/a |
| Mesalazine | 24 (4.8) | 34 (12.8) | 144 (57.4) | n/a |
| Azathioprine | 4 (0.8) | 8 (3.0) | 55 (21.9) | n/a |
| Mercaptopurine | 4 (0.8) | 1 (0.4) | 37 (14.7) | n/a |
| Methotrexate | 6 (1.2) | 5 (1.9) | 15 (6.0) | n/a |
| Corticosteroids | 35 (6.2) | 8 (3.0) | 35 (13.9 | n/a |
| Antibiotics | 30 (6.0) | – | – | |
| Ileostomy supplies | 266 (100) | | | |
| Hospitalization | 18 (3.6) | 19 (7.1) | 12 (4.8) | 0.10 |
| Surgery | 7 (1.4) | 3 (1.1) | 1 (0.4) | 0.45 |

CI, confidence interval; CT, computed tomography; MRI, magnetic resonance imaging; DXA, dual-emission X-ray absorptiometry; n/a, not applicable.
*Comparison between pouch and ileostomy

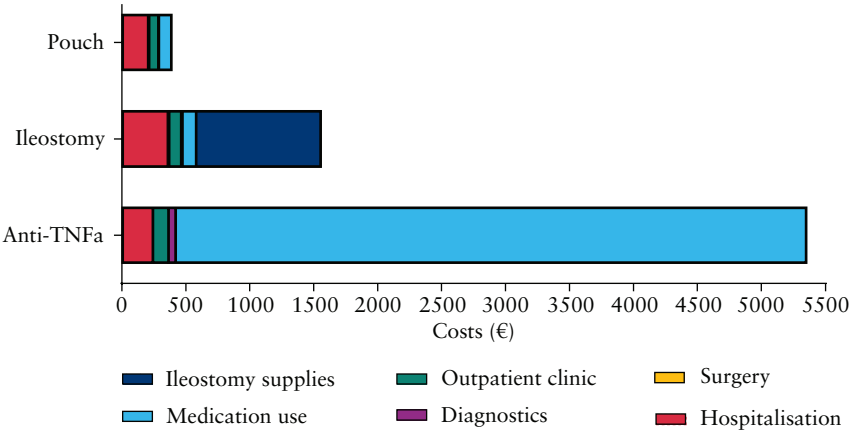


**Figure 2.** Mean 3-monthly healthcare costs of UC patients with a pouch, ileostomy and anti-TNFα therapy.

The high costs for patients on anti-TNFα therapy did not come as a surprise. We recently reported that anti-TNFα therapy, which was prescribed in just 4% of the 915 UC patients, was one of the major cost drivers, accounting for 31% of all healthcare costs.[2] Comparison with previous studies is difficult, because most studies were conducted in the pre-biological era. For example, a recent study from Olmsted County showed comparable healthcare costs in medically and surgically treated UC patients.[17] However, anti-TNF therapy was prescribed in only one patient and most patients were in clinical remission on conventional therapy, such as mesalazine and immunosuppressives. In line with our

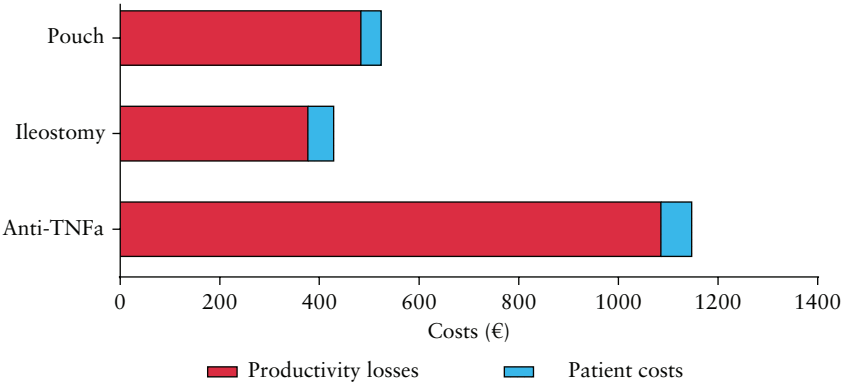


**Figure 3.** Mean 3-monthly productivity losses and patient costs of UC patients with a pouch, ileostomy and anti-TNFα therapy.

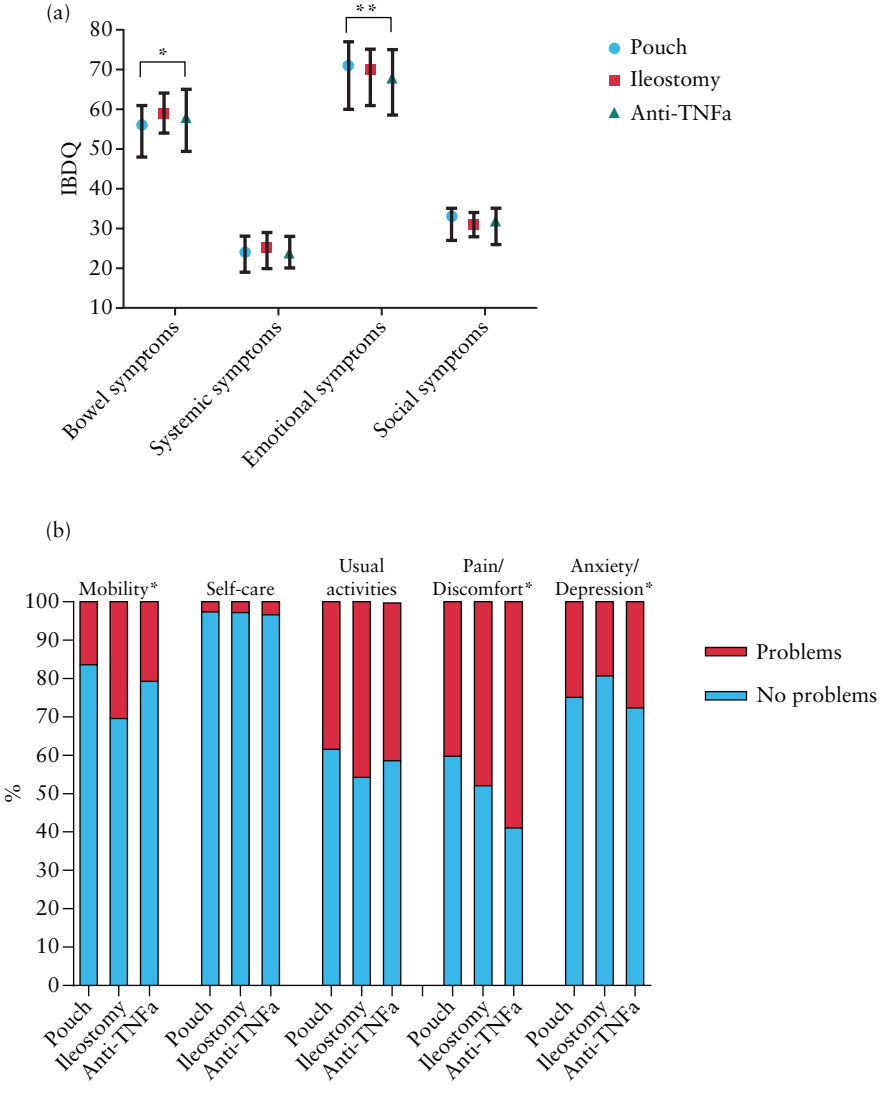


**Figure 4.** (A) IBDQ subscores in UC patients with a pouch, ileostomy and anti-TNFα therapy (median and IQR) (B) Proportion of reported problems (%) by EQ- 5D in UC patients with a pouch, ileostomy and anti-TNFα therapy.

data, the authors of this study found that end-ileostomy was associated with higher healthcare costs, even without taking ileostomy supplies into account. Reported cumulative frequency rates of pouchitis 10–11 years after ileal pouch - anal anastomosis (IPAA) surgery range from 23% to 46%.[18,19] In our study, only 17% of pouch patients reported bowel complaints in a window of 2 years of follow-up. Even if pouchitis was underrepresented in our cohort due to selection bias, this could not have explained the difference in costs between the two post-surgery groups.

Obviously, this observational study was not based on comparable groups of patients. Especially the differences in the post-surgery

groups and the patients receiving anti-TNFα therapy who still had disease activity preclude firm conclusions regarding the long-term consequences of the different treatment strategies. A randomized controlled trial would undoubtedly provide superior data, but will probably never be performed. Of note, in an earlier Olmsted County study a drop of almost 50% in healthcare costs was observed 2 years after surgery in UC patients who failed conventional therapy.[20] Obviously, a considerable decrease in healthcare costs is not anticipated in patients remission.

Productivity losses due to sick leave of paid work were the highest among patients on anti-TNFα therapy. These data should be interpreted with caution, given the differences in age and educational level between groups, with more anti-TNFα patients within the working age group. Evidently, disease activity played a major role in the loss of productivity in our patients, in particular in the anti-TNF-treated group, as reported previously.[12,21–23] Furthermore, we did not incorporate productivity losses due to work disability, as we did not know the cause of work disability. However, significantly more patients in the pouch and ileostomy groups were work-disabled, and therefore we have probably underestimated the productivity losses in these groups.

We found no differences in IBQD scores between the three groups. There are no studies in which quality of life has been compared between anti-TNFα therapy versus surgery. However, our findings are in line with a previous study in which quality of life was compared between ileostomy and pouch patients using the IBDQ.[24] However, employing the generic EQ-5D-3L, we found a difference between pouch and ileostomy patients. This is in contrast with previous studies (employing generic Short form health survey 36), in which no difference was found between pouch and ileostomy patients.[25,26] It could be that previous studies were underpowered to detect differences in quality of life. Looking at the absolute QALYs in pouch (0.90) and ileostomy (0.84) patients, one might conclude that the overall quality of life in the surgery group was good.

Due to our study design, the outcome could be biased by patient preferences. Patients with UC occasionally decline restorative surgery after subtotal colectomy for a number of reasons, such as the risk of decreased fecundity in young women, the risk of recurring pouchitis or perioperative complications, while patients with a pouch often put up with the disadvantages and potential complications of a pouch because an ileostomy is not acceptable to them.

The strength of our study is the uniqueness of our cost data and the detailed characterization of the patients and their cost profiles. Our findings might help to guide clinical decision-making in UC patients who fail conservative medical therapy and may be used for economic modelling. An important limitation of our study was the risk of confounding by indication. This is due to the fact that patients were not randomized for surgery or medical treatment. A randomized controlled trial would undoubtedly provide superior data, but will probably never be performed since most physicians consider pouch reconstruction the procedure of choice as reflected in the majority of international guidelines. To underscore the internal validity of our cohort, we performed a non-responder survey, and found no differences between responders and non-responders, as previously published.[2]

In conclusion, this is the first study aiming to provide an integrated assessment of healthcare use, work absenteeism and associated costs, and quality of life in UC patients with an ileostomy or pouch or on anti-TNFα therapy. Despite some shortcomings, we were able to demonstrate that UC patients treated with anti-TNFα therapy had the highest healthcare expenditures. Remarkably, patients with an ileostomy had higher healthcare costs compared with patients with a pouch.

## Funding

This study was supported by an unrestricted grant from Abbvie.

## Conflict of Interest

MvdV has no competing interests. MJM declares fees paid by GSK to the institution for participating in model building (pertussis). AvB has acted as a consultant for Ferring, Abbott and MSD and received payments for lectures from Abbott and Ferring. HF has acted as a consultant for Abbott. DdJ has acted as a consultant for Synthon Netherlands and received payments for lectures from Abbott, Ferring and MSD. MP has acted as a consultant for MSD and received payments for lectures from MSD, Falk Pharma, Abbvie and Ferring. GD has no competing interests. JvdW has acted as a consultant for Abbott, Ferring, Shire and MSD and received payment for lectures from Abbott, Falk Pharma and MSD. MRC has no competing interests. CC has no competing interests. JM has acted as a consultant for Abbvie, MSD, Ferring and Falk and received payments for lectures for Abbvie and MSD. PvdM has no competing interests. CYP has acted as a consultant for Abbott and received payments for lectures from Ferring and MSD. CB has no competing interests. RV has no competing interests. AvdM has acted as consultant for Abbott, MSD, Ferring and Dr Falk and received payments for lectures from Abbott and MSD. PS has no competing interests. ML has no competing interests. BO has acted as a consultant for Abbott, Takeda and MSD and received payment for lectures from Ferring, MSD and Abbvie.

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## Author Contributions

Conception and design of the study: MvdV, BO, MJM. Acquisition of data: MvdV, BO, MJM. Analysis and interpretation of data: MvdV, BO, MJM, ML. Drafting the article: MvdV. Critical revision of the article: all authors. Final approval of the article: all authors.

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