Journal of Inflammatory Bowel Diseases & Disorders

Connelly et al., J Inflam Bowel Dis & Disord 2016, 1:1

Research article Open access

# Genetic and Demographic Correlates of Quality of Life after Ileal Pouch Anal Anastomosis for Ulcerative Colitis

**Tara M Connelly, Bailey Sanders, Arthur S Berg, Emmanuelle Williams, Leonard Harris III, Andrew Tinsley, Walter A Koltun***

*College of Medicine, The Pennsylvania State University, Hershey, United States*

***Corresponding Author:** Walter A Koltun, Division of Colon and Rectal Surgery, Department of Surgery, College of Medicine, The Pennsylvania State University, Hershey, PA, USA, Tel: 7175315164; Fax: 717 5310646; Email: wkoltun@hmc.psu.edu

**Received date:** April 19, 2016; **Accepted date:** May 18, 2016; **Published date:** May 24, 2016



## Abstract

**Objective:** Patient satisfaction after ileal pouch anal anastomosis (IPAA) for ulcerative colitis (UC) is difficult to predict preoperatively and has never been investigated from a genetic perspective.

**Methods:** Modified IBD quality of life (QOL) questionnaires were mailed to all UC-IPAA patients in our IBD Biobank. Genotyping was performed using a custom microarray containing 325 IBD-associated single nucleotide polymorphisms (SNPs). Fisher's exact and Mann-Whitney tests and logistic regression with the Bonferroni correction were used for analysis.

**Results:** Response rate was 69% (142 of 206 patients, mean pouch duration=10.1 ± 0.5years). Patients diagnosed at a younger age and with shorter time to colectomy reported poorer emotional wellbeing scores. Readmission post-colectomy was significantly associated with poor overall and emotional scores. On multivariate analysis, female gender and readmission were predictors of poor overall QOL. Poorer emotional wellbeing and systemic symptom scores were found in patients who had undergone colectomy urgently. Smoking history correlated with poor bowel and social scores. SNP rs2279627 associated with the immunoregulatory *TNFSF14* gene and two *POU5F1/OCT4* gene related SNPs, rs7837328 and rs7014346, were significantly associated with poorer emotional wellbeing scores. Rs2279627 was also significantly associated with poorer scores in the overall and bowel symptom categories.

**Conclusions:** 1) Female gender, short duration between diagnosis and colectomy and younger age at diagnosis were predictors of poor QOL post-IPAA. 2) Three SNPs were identified as potential genetic predictors of low scores in the bowel symptoms, emotional wellbeing and overall QOL categories. These findings may be used to identify and council patients at risk for dissatisfaction post-IPAA.

## Key words:

Ulcerative colitis; IPAA; Quality of life; Genetics; *TNFSF14*

## Introduction

Total proctocolectomy (TPC) with ileal pouch anal anastomosis (IPAA) is the operation of choice for ulcerative colitis (UC) patients with medically refractory symptoms, steroid dependence and/or dysplasia or cancer [1]. The IPAA constructs a functional reservoir using a length of small bowel folded over to create a neorectum and attaches it to the preserved sphincters to maintain continence. Overall, this operation has a high rate of patient satisfaction [2-9]. However, a subgroup of patients experience poor quality of life (QOL) after pouch creation with continued physical symptoms and/or a decrease in emotional or social QOL. Although it has been suggested that females and those with pouchitis or inflammation of the pouch are generally unhappier after IPAA, results are conflicting and confounded by the inclusion of patients with indeterminate colitis and Crohn's disease. Presently, there are few studies identifying clear clinical or histological variables that can predict poor pouch outcome to aid in surgical decision making preoperatively. The biopsychosocial model of inflammatory bowel disease (IBD) takes physical symptoms and social and emotional well-being into consideration [10]. A strong emotional component to IBD patient QOL and the negative emotional effect of the unpredictable nature of IBD was evidenced in a survey of 320 Crohn's and Colitis Foundation of America (CCFA) members with IBD who cited their primary concern as being 'the uncertain nature of their disease.' This concern was greater than fear of surgery, developing cancer, pain, suffering, attractiveness and losing bowel control [11]. This sentiment may similarly play a role in UC patients after IPAA. The inflammatory bowel disease questionnaire (IBDQ) is the most commonly used IBD-specific, validated questionnaire given to UC and CD patients to assess their QOL/overall satisfaction in 4 distinct areas: systemic symptoms, bowel symptoms, social wellbeing and emotional wellbeing [12]. The aims of the present study were to:

Identify clinical features associated with differences in overall quality of life after IPAA and in 4 distinct subcategories: 1) Bowel symptoms, 2) Systemic symptoms, 3) Emotional wellbeing and 4) Social wellbeing, using a modified IBDQ.

Correlate the QOL in these categories with genetic polymorphisms that may possibly identify IPAA patients who are at 'high risk' of poor quality of life after IPAA. Such 'genetic predictors' may then potentially be used preoperatively to predict patient satisfaction with the IPAA and possibly assist in surgical decision making.

## Materials and Methods

All recruited patients who had undergone TPC and IPAA between Jan 1990 and Jan 2013 were identified from the Hershey Medical Center Division of Colon and Rectal Surgery Internal Review Board approved IBD Biobank. This Biobank, established in 1998, contains demographic and clinical data, isolated DNA, immortalized B cell lines [13]. Serum and tissue specimens from over 1,800 sporadic and familial IBD patients and their unaffected relatives as well as controls in the form of patients with diverticulitis, colorectal cancer, slow transit, colonic trauma, polyposis syndromes and healthy volunteers. All IBD patients are advised of the registry and are given the option to participate when presenting to our IBD center. After informed consent is obtained, a blood sample is taken and DNA is isolated using a QiagenR DNA Blood Midi kit (Qiagen Inc. Valencia, CA) following the manufacturer's recommended protocol. For the present study, only patients over the age of 18 at the time of the questionnaire mailing were included and those who had undergone pouch excision (n=5) were excluded. At the time of this study 206 UC patients with an IPAA were in the Biobank and eligible for study.

## Questionnaire Design

A 42 item questionnaire customized for IPAA patients was developed based upon a modified version of the established, validated IBD Quality of Life Questionnaire (IBDQ) [14-16]. The IBDQ is a 32 item survey covering 4 main areas: 1) Bowel symptoms, 2) Systemic symptoms (including fatigue, general malaise, sleep, weight maintenance and energy), 3) Social wellbeing and 4) Emotional wellbeing which has been previously validated in IPAA patients [17, 18]. Questionnaire answers are provided in terms of frequency, i.e., how often do you feel sad (all of the time, most of the time, often, some of the time, rarely, never) which can be formatted into a corresponding numerical score with 1 as the worst score and 7 as the best, resulting in a minimum score of 32 and a maximum score of 224 [19]. UC patients in remission typically score around 190 [12]. For the present study, each question in the IBDQ was qualified with the preamble "Since you had your pouch operation." Questions on stool frequency, stool urgency, rectal bleeding, antibiotic and steroid use were correlated with QOL scores in each of the 4 QOL categories along with the demographic and operative details described below. The questionnaire was mailed to all recruited IPAA patients in the Biobank with a self-addressed stamped envelope enclosed. A second mailing to all non-respondents (n=106) was performed 6 weeks after the initial mailing. A thorough retrospective review of all respondents' charts was undertaken. Patient demographics (including gender, family history of IBD, smoking status, presence of primary sclerosing cholangitis (PSC), age at diagnosis, age at colectomy, American College of Anesthesiology (ASA) score at the time of the IPAA and Charlson comorbidity score [20]. operative details (including elective *vs* urgent status of colectomy, indication for colectomy (medically refractory disease or cancer/dysplasia), duration between diagnosis and colectomy, length of stay post colectomy, postoperative complications using the Clavien-Dindo score) [21]. open *vs.* laparoscopic approach, number of operative stages in the IPAA (1, 2, modified 2 or 3) and pouch specific details (pouch duration and pouchitis history) were recorded.

## Genotyping

DNA was extracted from fresh blood as described above. When DNA from fresh blood was not available, DNA was extracted from previously immortalized B cell lines [13]. Patients' DNA was genotyped on the HMC Division of Colon and Rectal Surgery's custom designed IBD Illumina Bead Express SNP chip (Illumina, San Diego, CA). This chip was developed through a series of extensive literature searches and contains 348 IBD and/or colorectal cancer (CRC) associated SNPs (93 CD, 49 UC, 183 both UC and CD, 23 CRC). SNPs on this chip have been reported elsewhere [22]. A spectrophotometer was used to quantify DNA concentrations and 10 ng/μL working stocks were prepared in 10 mm Tris-HCl. A Quant-iT™ PicoGreen® dsDNA Assay Kit (Invitrogen, Carlsbad, CA) was then used to quantify dsDNA concentrations for specimen optimization prior to chip application. The chip was then run in the Penn State Hershey Medical Center Functional Genomics Core Facility on an Illumina BeadXpress Reader.

## Statistics

For questionnaire analysis, answers were converted into corresponding numerical scores and a median value for each category (bowel symptoms, systemic symptoms, emotional wellbeing, social wellbeing and overall score) based on all patient response scores was calculated. Individual patient responses in each category were then divided into high/low values based on the respective calculated median values of the groups in each comparison. Fisher's exact test and the Mann-Whitney U test were used for the categorical and continuous variables respectively. All values are presented with standard deviation (SD) where appropriate. Each of the noncontinuous non-genetic variables with a P value $\leq 0.05$ in each category were then entered into a multivariate analysis for that category. Values are presented with SD where appropriate. For the current project, only SNPs with a minor allele frequency (MAF)>5% and SNPs for which >90% of patients had a definitive genotype call when analyzed by the Illumina reader were included for statistical evaluation. The final number of SNPs analyzed was 307. Logistic regression with a Bonferroni correction to adjust for multiple comparisons of 307 SNPs was used for the genetic analysis. R software was used for all analyses.

## Ethical Considerations

All participants were voluntary participants in our Institutional Review Board approved IBD Biobank. Questionnaires were returned voluntarily and stored securely in our IBD research lab. Data from questionnaires were correlated with genetic results using previously assigned numeric identifiers so that investigators recording questionnaire results were blinded to the patients' identities.

## Results

### Demographics

Two hundred and six IPAA patients were identified and mailed surveys. Fourteen surveys were returned 'addressee unknown' and 142 were returned completed for a response rate of 69%. Demographics are shown in Table 1. The respondents were 61% male (86/142). The majority (80%, 114/142) did not have a family history of IBD. Fifty-five were former smokers and 3 were current smokers. Due to the small number of current smokers, the current and former smokers were grouped together for analysis and thus results are most reflective of former smokers. The majority of colectomies were performed electively (83%) with 13 of these elective colectomies performed for UC associated CRC or dysplasia. Ten patients (7%) had a concomitant

diagnosis of PSC. Average length of stay at the time of colectomy was 7.8 ± 4.3 days. Mean age at UC diagnosis and pouch operation were 31.8 ± 11.6 and 50.5 ± 12.4 years respectively. The average pouch duration of the group was 10.1 ± 5.8 years (range 0.5-23.2 years) and average time between UC diagnosis and colectomy was 7.9±8.1 years. Of note, only 1 patient had a pouch of 6 months' duration. The next 'youngest' pouch was 1 year's duration in 3 patients. Seventy-nine (55.6%) reported having at least 1 episode of pouchitis. Twenty-three (23%) of patients were taking IBD or pouch related medication at the time of the survey (Table 2).

| | Number | Percent |
|---|---|---|
| Male | 86 | 61% |
| Smoker current/ex | 3 current/55 ex | 41% |
| Family history of IBD | 28 | 20% |
| Primary sclerosing cholangitis | 10 | 7% |
| Urgent colectomy | 24 | 17% |
| 30 day readmission post IPAA | 26 | 19% |
| Currently taking medication for IBD | 33 | 23% |
| Age at diagnosis (years, SD) | 31.8 ± 11.6 | NA |
| Pouch duration (years, SD) | 10.1 ± 5.8 | NA |
| Age at pouch operation (years, SD) | 41.09 ± 11.6 | NA |
| Duration between diagnosis and colectomy (years, SD) | 7.9 ± 8.1 | NA |
| Length of stay at colectomy (days, SD) | 7.8 ± 4.3 | NA |
| Clavien-Dindo 0:1:2:3a/b | 70:29:16:11 | NA |

**Table 1:** Respondent demographics.

| | Number of patients reporting use at the time of questionnaire |
|---|---|
| Antibiotics | 5 (3.5%) |
| 6MP/AZA | 6 (4.2%) |
| Cholestyramine | 1 (.7%) |
| Diphen/atropine,loperamide | 10 (7%) |
| TNF antagonists | 6 (4.2%) |
| Steroids | 1 (.7%) |
| Steroids + AZA | 1 (.7%) |
| Steroids + antibiotics | 1 (.7%) |
| Steroids/TNFantagonist | 2 (1.4%) |

**Table 2:** Medical treatment at time of questionnaire completion; **MP**= Mercaptopurine; **AZA**=Azathioprine; **TNF**=Tumor Necrosis Factor.

## Univariate questionnaire results

Overall QOL: Women had poorer overall QOL scores with 66% scoring below the median (P=0.003) (Figure 1). Postoperative complication details were available for 126 patients. The remaining 16 patients had their procedure performed at an outside institution and complication details were not available. Although no significant difference in overall QOL was demonstrated between those with no, minor (Clavien-Dindo I/II) or major complications (Clavien-Dindo IIIa/b) in overall QOL scores or in any of the 4 subcategories, readmission within 30 days was associated with poorer scores (69% scoring below the median P=0.05).

The most significant association with low overall QOL scores was a history of pouchitis (P=0.00008). Sixty-six per cent of pouchitis patients reported lower than median scores (*vs.* only 26% of those who reported never having pouchitis). Antibiotic or steroid use was associated with worse scores, with 59.8% and 80% of patients taking

those drugs respectively having less than median scores (P=0.03 and 0.05). Lower scores were reported by 100% of the 4 patients who reported fecal urgency (P=0.004). Interestingly, 85.7% of 14 patients who reported intermittent pyrexia fell below the median (P=0.009).

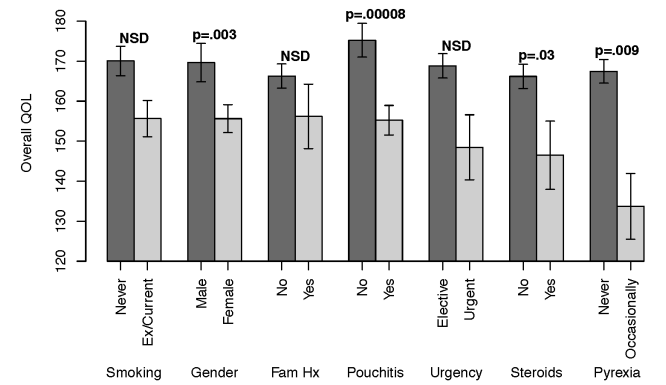


**Figure 1:** Overall QOL scores on univariate analysis. Univariate analysis of overall QOL demonstrated female gender, intermittent pyrexia, pouchitis and steroid use to be significantly associated with poorer overall QOL. Readmission within 30 days of colectomy was also associated with poorer overall QOL scores (not shown).

Bowel symptoms: The most significant association with poor bowel symptom scores (indicating more severe or frequent symptoms) was a history of smoking (Figure 2). Seventy-two percent of ex/current smokers reported low scores compared to 41% of never smokers (P=0.0003). Also significantly associated with poor Bowel Symptom scores were a diagnosis of pouchitis or steroid use. However, there was no association with antibiotic use. Not surprisingly, those with frequent fecal urgency had significantly worse scores as did those who experienced intermittent pyrexia. Factors that were present prior to IPAA found to be associated with poorer bowel symptom scores were shorter duration between UC diagnosis and colectomy (3.3 ± 7.3 years in those below the median score vs 6.8±8.7 above the median, P=0.04) and PSC (P=0.04)

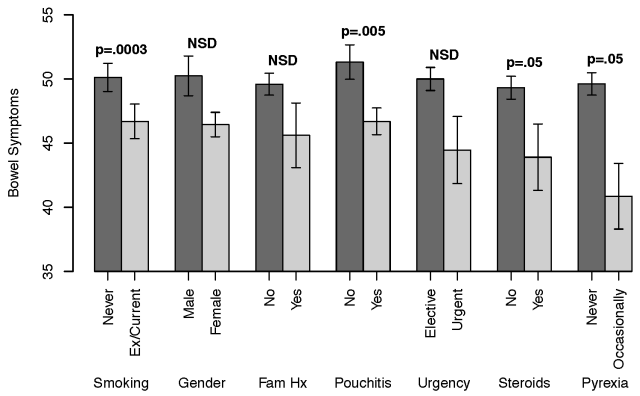


**Figure 2:** Bowel symptoms scores on univariate analysis. A smoking history, pouchitis, steroid use and intermittent pyrexia were associated with lower scores in the bowel symptoms category indicating more severe symptoms. Also significantly associated with poor scores was a short duration between UC diagnosis and colectomy (not shown).

Emotional wellbeing: The most significant association with poor emotional wellbeing scores was a history of an urgent (*vs.* elective) colectomy (P=0.006) (Figure 3). Seventy-five percent of the 24 urgent colectomy patients *vs.* 43.3% of the 118 elective patients reported low (below median) emotional wellbeing scores (P=0.006). Other significant potential predictors present prior to IPAA in this category included younger mean age at colectomy and a shorter duration between UC diagnosis and colectomy (mean of 6.6 ± 7.4 *vs.* 9.3 ± 8.6 years, P=0.05). PSC was significantly associated with higher emotional wellbeing scores. Pouchitis, steroid use, antibiotic use, the frequent need to rush to the bathroom and 30 day readmission were also associated with lower emotional wellbeing scores.

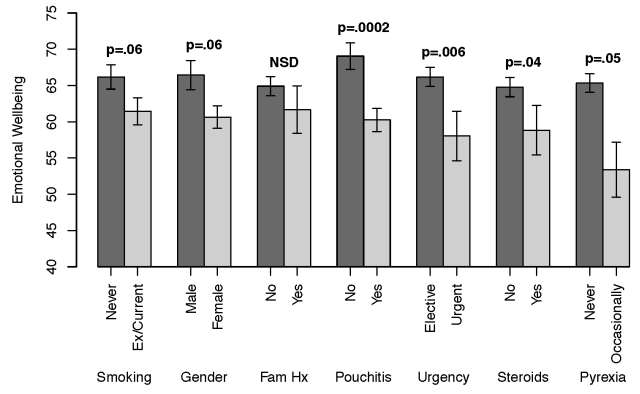


**Figure 3:** Emotional wellbeing scores. A colectomy performed urgently (*vs.* electively), pouchitis, urgency, steroid use and intermittent pyrexia were significantly associated with lower emotional wellbeing scores. Also significantly associated with poor scores was a short duration between UC diagnosis and colectomy, readmission within 30 days of colectomy and a younger age at pouch operation (not shown).

Social wellbeing: A smoking history was the only demographic factor significantly associated with low social wellbeing scores (Figure 4). Taking any UC medication at the time of questionnaire completion, fecal urgency, a history of pouchitis or intermittent pyrexia were also associated with poorer social wellbeing scores (P=0.05, 0.008, 0.02 and 0.02 respectively).

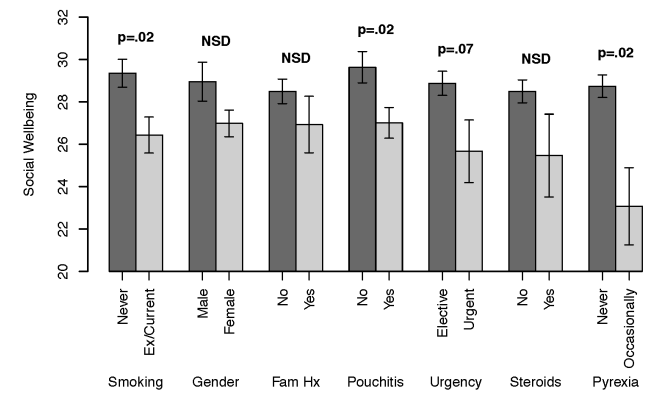


**Figure 4:** Social wellbeing scores. Female gender, a smoking history, pouchitis and pyrexia were associated with poorer social wellbeing scores.

Systemic Symptoms:Factors present prior to IPAA associated with increased systemic symptom complaints included female gender, urgent colectomy and ex/current smoking status (Figure 5). A history of pouchitis and steroid use after IPAA use were associated with scores significantly below the median in the systemic symptom category, indicating more severe and frequent systemic symptoms. Those taking any medication for IBD at the time of questionnaire were twice as likely to score below the median. Fecal urgency and intermittent pyrexia, not unexpectedly, were associated with worse systemic symptoms.

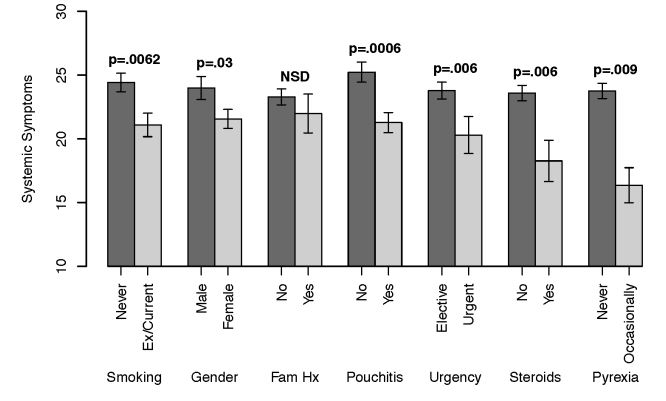


**Figure 5:** Systemic symptom scores. Lower systemic symptom scores, reflective of more frequent and severe systemic symptoms were found in females and patients with a smoking history, pouchitis, urgency, steroid use and intermittent pyrexia.

Genetic results: Although several SNPs were initially associated with high or low scores in each category, only 3 SNPs associated with 2 genes, tumor necrosis superfamily *(TNFSF)14* and POU domain, class 5, transcription factor 1 (*POU5F1B*) retained significance after Bonferroni correction (Table 3). The *TNFSF14* SNP, rs2279627, was initially significantly associated with all 5 QOL categories. However, it only remained statistically significant in the overall QOL, bowel symptom and emotional wellbeing categories after Bonferroni correction (Table 3). For rs2279627, the C allele was the demonstrated risk allele for poor scores in all QOL categories. Over 60% of CC homozygotes scored below the median in each of the 3 categories (Table 4). Two POU5F1 SNPs (rs7837328, rs7014346) retained significance in the emotional wellbeing category. The A allele was the poor QOL risk allele in both POU5F1 SNPs with over 70% AA homozygotes for both SNPs having emotional wellbeing scores below the median (Table 5).

| SNP | Gene | P-value | Bonferroni corrected P-value |
|---|---|---|---|
| **SNPs associated with overall QOL** | | | |
| rs2279627 | TNFSF14 | 0.0001 | 0.033 |
| rs7837328 | 8q24 | 0.00034 | NSD |
| rs7014346 | 8q24 | 0.0018 | NSD |
| rs7712957 | S100Z | 0.002 | NSD |
| **SNPs associated with bowel symptoms** | | | |
| rs2279627 | TNFSF14 | 0.0001 | 0.033 |
| rs7712957 | S100Z | 0.0004 | NSD |
| rs1297265 | Gene desert | 0.002 | NSD |
| rs9647373 | CLDN1 | 0.005 | NSD |
| **SNPs associated with emotional wellbeing** | | | |
| rs7837328 | POU5F1 | 0.00002 | 0.0061 |
| rs2279627 | TNFSF14 | 0.00014 | 0.046 |
| rs7014346 | POU5F1 | 0.00014 | 0.0146 |
| rs7712957 | S100Z | 0.002 | NSD |
| **SNPs associated with social wellbeing** | | | |
| rs2279627 | TNFSF14 | 0.013 | NSD |
| rs1547832 | CGN | 0.020 | NSD |
| rs1004819 | IL23R | 0.020 | NSD |
| rs7837328 | 8q24 | 0.021 | NSD |
| **SNPs associated with systemic symptoms** | | | |
| rs2279627 | TNFSF14 | 0.0019 | NSD |
| rs1004819 | IL23R | 0.0033 | NSD |
| rs615969 | ZO-1 | 0.0035 | NSD |
| rs13073817 | Gene desert | 0.004 | NSD |

**Table 3:** Single nucleotide polymorphism correlations with quality of life parameters.

| **SNP genotype/Patient group** | | |
|---|---|---|
| **Overall QOL** | Above the median n=68 | Below the median n=66 |
| CC n=75 | 29 (39%) | 46 (61%) |
| CG n=51 | 35 (69%) | 16 (31%) |
| GG n = 8 | 4 (50%) | 4 (50%) |
| **Bowel symptoms** | Above the median n=63 | Below the median n=71 |
| CC n=75 | 30 (40%) | 45 (60%) |
| CG n=51 | 27 (53%) | 24 (47%) |
| GG n=8 | 6 (75%) | 2 (25%) |
| **Emotional wellbeing** | Above the median n=63 | Below the median n=68 |
| CC n=75 | 28 (37%) | 47 (63%) |
| CG n=51 | 33 (65%) | 18 (35%) |
| GG n=8 | 5 (62.5%) | 3 (37.5%) |

**Table 4:** Rs2279627 genotypes.

| **SNPgenotype/ Patient group** | | |
|---|---|---|
| **rs7837328** | **Above the medium n=63** | **Below the median n=58** |
| AA n=19 | 5 (26%) | 14 (74%) |
| AG n=54 | 26 (48%) | 28 (52%) |
| GG n=47 | 31 (66%) | 16 (34%) |
| rs7014346 | Above the median n=66 | Below the median n=68 |
| AA n=14 | 3 (21%) | 11 (79%) |
| AG n=49 | 24 (49%) | 25 (51%) |
| GG n=57 | 35 (61%) | 22 (39%) |

**Table 5:** Emotional wellbeing POU5F1 SNP genotypes for rs7837328 and rs7014346.

On multivariate analysis, female gender, a 30 day postoperative readmission, pouchitis and intermittent pyrexia remained as independent predictors of poor overall QOL scores (Table 6). Pouchitis after IPAA was an adverse indicator of QOL in all subcategories. Ex/current smoking was associated with poor bowel and social wellbeing. Urgent colectomy was associated with poor emotional wellbeing and systemic symptoms. Fecal urgency remained associated with poor bowel symptom scores and steroid use with poor systemic symptom scores.

| | **Univariate analysis Univariate analysis** | **Multivariate analysis** | | |
|---|---|---|---|---|
| | P-value | OR | 95% CI | P-value |
| **Overall QOL** | | | | |
| Female gender | 0.003 | 2.6 | 1.1-6.0 | 0.02 |
| Readmission within 30 days post colectomy | 0.05 | 5.3 | 1.8-16.7 | 0.005 |

| | | | | |
|---|---|---|---|---|
| History of pouchitis | 0.00008 | 5.6 | 1.12-20 | 0.003 |
| Intermittent pyrexia | 0.009 | 5.9 | 1.3-50 | 0.03 |
| Intermittent steroid use | 0.03 | | | |
| Intermittent antibiotic use | 0.04 | NSD | | |
| Urgency | 0.004 | | | |
| **Bowel symptoms** | | | | |
| Ex/current smoker | 0.003 | 1.4 | 1.45-7.18 | 0.003 |
| History of pouchitis | 0.004 | 2.6 | 1.23-5.8 | 0.01 |
| Urgency | 0.0005 | 3.1 | 1.4-7.14 | 0.006 |
| Intermittent steroid use | 0.035 | | | |
| Intermittent pyrexia | 0.0005 | NSD | | |
| **Emotional wellbeing** | | | | |
| Readmission within 30 days post colectomy | 0.05 | 5.5 | 1.8-20.0 | 0.004 |
| History of pouchitis | 0.00002 | 5.3 | 1.7-20 | 0.007 |
| Urgent colectomy | 0.006 | 3.6 | 1.2-12.5 | 0.02 |
| PSC* | 0.05 | | | |
| Intermittent antibiotic use | 0.04 | | | |
| Urgency | 0.007 | | | |
| Intermittent steroid use | 0.03 | NSD | | |
| Intermittent pyrexia | 0.05 | | | |
| **Univariate and multivariate analyses for social wellbeing** | | | | |
| Ex/current smoker | 0.02 | 1.5 | .99-4.46 | 0.053 |
| History of pouchitis | 0.02 | 2.12 | 1.0-4.3 | 0.04 |
| Urgency | 0.007 | | | |
| Intermittent pyrexia | 0.02 | NSD | | |
| Systemic symptoms | | | | |
| Urgent colectomy | 0.0063 | 3.22 | 1.1-11.1 | 0.037 |
| History of pouchitis | 0.0006 | 2.27 | 1.0-5.2 | 0.046 |
| Intermittent steroid use | 0.0005 | 4.55 | 1.0-1.8 | 0.03 |
| Female gender | 0.03 | | | |
| Ex/current smoker | 0.0003 | | | |
| Urgency | 0.01 | NSD | | |
| Intermittent pyrexia | 0.009 | | | |

**Table 6:** Univariate and multivariate analyses of all QOL parameters.

## Discussion

Previous studies have investigated QOL after IPAA, and those, like the present study, have demonstrated that QOL most significantly relates to pouch function, e. g: number of bowel movements, pouchitis and urgency. However, less well studied are the preoperative factors that will predict post-IPAA QOL. Thus, the present study is unique in two ways:

1) We sought to identify predictors of poor QOL and would be either modifiable before proceeding with IPAA or easily identified for incorporation into the decision making process when evaluating a UC patient as a potential candidate for the procedure. 2) The identification of possible genetic predictors of poor QOL after IPAA. Never before have genetic factors been studied to assess patient satisfaction with a surgical procedure. Factors we identified as associated with poor QOL on univariate analysis included; female gender (overall QOL and systemic symptoms), a smoking history (bowel symptoms, social wellbeing and systemic symptoms), short duration between UC diagnosis and colectomy (bowel symptoms and emotional wellbeing), urgent colectomy (emotional wellbeing and systemic symptoms), readmission within 30 days of colectomy (overall QOL and emotional wellbeing) and a younger age at pouch operation (emotional wellbeing). On multivariate analysis, female gender and a 30 day readmission were demonstrated to be independent predictors of low overall QOL scores. A smoking history remained associated with poor bowel symptom and social wellbeing scores. Urgent colectomy was independently associated with poor emotional wellbeing scores. Female gender, smoking history and urgent colectomy are the only factors that are present prior to pouch creation and as such might be considered as prognostic factors preoperatively. Of the several QOL scoring systems, the IBDQ has the most extensive coverage of the subcategories most pertinent to patient QOL after IPAA, namely, emotional, social, bowel and systemic categories. The IBDQ has been validated both in UC [16] and IPAA patients [18]. Importantly, it is relatively easy to complete thus making it suitable for a mail survey and thus was chosen for the present study. The statistical method of evaluating patient scores as above or below the median was chosen to provide a general idea of which patients were faring better or worse than average in each category, a more clinically useful measurement than a raw score. Postoperative pelvic sepsis, pouchitis and functional pouch related problems such as urgency and frequency have been repeatedly shown to be associated with poor QOL post-IPAA [23-26]. Thus our finding of decreased QOL in all categories in patients with pouchitis and/or urgency is similar to results seen in studies by Andersson [27]. Fazio [28]. and Koerdt which are, in combination, inclusive of over 5,000 patients [24]. The majority of post IPAA QOL studies have recorded QOL using mainly subjective measures such as limitations in social activities and recreation, incontinence, sexual function, and dietary restrictions [28-29]. Such QOL measurements cannot be used preoperatively to predict QOL and are not helpful when trying to choose the appropriate candidate for an IPAA. Additionally, these measures do not reflect emotional and social wellbeing accurately as two patients with the same symptoms may experience very different emotional responses. Thus, the present study sought to capture predictors of QOL that are present preoperatively and correlate with IPAA patients' assessment of their own QOL. Degree of rectal mucosal inflammation, which can be measured Preoperatively, has been correlated with increased postoperative complications in pediatric patients. However, a correlation with QOL has not yet been studied [30]. Factors that could confound QOL results include comorbidities other than IBD. There was no difference in QOL scores between the different ASA, Charlson comorbidity and Clavien-Dindo postoperative complication categories, suggesting that comorbidities, overall health status and postoperative complications did not separately affect QOL. This is consistent with data from a very large study of 3700 pouches (including CD and CRC pouches) which demonstrated that despite a 66% comorbidity rate, 96% of IPAA patients were happy [28]. Additionally, the number of stages or operations utilised to achieve the result of colectomy with functioning IPAA and no ileostomy varied in the group. Ten patients underwent a 1 stage procedure in which no defunctioning ileostomy is required. Sixty-two underwent a 2 stage, 37 underwent a modified 2 stage (colectomy followed by IPAA without ileostomy) and 17 underwent a 3 stage procedure. There was no difference in any of the QOL scores when these 4 groups were considered individually or grouped as 1/2 *vs.* mod 2/3. As the aim of the study was not to find a genetic predictor of pouch dysfunction (e. g., pouchitis), but instead QOL, lack of replication of association with the SNPs previously associated with pouchitis is not unexpected [31]. However, a member of the TNFSF superfamily, *TNFSF14,* was found to be associated with worse QOL. The members of the *TNFSF* superfamily play a key role in regulating the immune response particularly in T cell activation and differentiation. The SNP associations discovered in the present study are relatively robust because they were derived from an analysis of over 300 SNPs and have withstood a Bonferroni correction. The genes associated with these SNPs can presumably affect QOL due to their roles in the disease pathogenesis. The *TNFSF14* gene is part of the tumor necrosis factor superfamily and its main role is in in the adaptive immune system and functions via the NFkB pathway. The transmembrane protein product of the gene, also known as LIGHT, is expressed by activated T lymphocytes, immature dendritic cells, monocytes and granulocytes. Increased expression has been demonstrated to be associated with tissue destruction and autoimmune-like diseases [32,33]. LIGHT has been suggested to mediate the VEGF-induced apoptosis of macrophages during wound healing, which is critical to the resolution of inflammation [34]. The *TNFSF14*/LIGHT protein is involved in the stimulation of T cell proliferation, genetic and demographic correlates of QOL after Ileal Pouch which is particularly important for the survival of CD4+ memory T cells [35]. Increased LIGHT expression has been demonstrated in T cells from the mucosa of IBD patients and experimental mice with increased LIGHT expression by T cells have been shown to develop colitis [36]. However, how this gene and its associated pathophysiology (as opposed to other genes) specifically translates into an altered or worse QOL after IPAA is not perfectly clear. The present study simply implicates its association with a poorer QOL post-IPAA. The POU5F1 gene, also known as the Octamer-Binding Transcription Factor 4 *(OCT4)* gene, plays a role in embryonic development and is required for embryonic stem cell pluripotency and adult stem cell renewal. Its product is a nuclear protein. This gene has been associated with colonic adenomas [37] and has been found to be expressed in colorectal cancer cell lines [38]. In a mouse model with inducible *OCT4* expression, dysplastic lesions of the large and small intestine developed when the gene was induced. The authors of the study found that *OCT4* potentially contributes to oncogenesis by inhibiting the differentiation of dividing progenitor cells [39]. Little study of this gene in IBD patients has been done. However, in a recent study of UC and sporadic CRC tissue, POU5F1 expression levels were found to be significantly higher in inflamed UC epithelial tissue without cancer than UC tissue with cancer [40]. Although this gene is associated with colorectal cancer, there was no significant association with UC-CRC in our cohort (P>0.05) as the 13 included UC-CRC/

dysplasia patients were of equal mixed homozygous wildtype, heterozygous and homozygous risk genotypes for this SNP. Similarly, how this gene may impact on pouch function and eventual patient satisfaction is unclear. It remains to be clarified if the SNP associations demonstrated in the present study are predictors of physiologic consequences (e.g. pouchitis, pyrexia, or urgency) that together correlate with a poorer QOL. These SNPs may not work through a physiologic correlate however, but instead be markers for other less well defined processes (psychologic, for example) that have effects on perceived personal wellbeing. The biologic explanation of these SNP correlations can likely be explained by the current etiologic theory of IBD, namely an interplay between host and environment on a background of genetic predisposition. This theory has been extended to disease phenotype in the past in terms of disease location, disease behaviour and very likely may also explain QOL. At the current time, utilizing genetic results to council patients on surgical outcomes is not routinely practiced. Thus utilizing these SNP associations alone to predict post IPAA QOL is not appropriate at this time as these SNP associations should be replicated in an additional study cohort. Some unexpected study findings include better reported QOL in PSC patients. Larger studies have demonstrated poorer overall QOL in these patients when compared to UC-IPAA patients without pouchitis [41]. However, only 10 patients in the present study had PSC. Results may be different in a larger cohort. Also unexpected was the lower social and emotional wellbeing scores in those with a family history of IBD, a situation where more support and a knowledge of the disease course may be present. Although intermittent steroid and antibiotic use were both associated with poorer overall QOL, only steroids were associated with poorer emotional wellbeing and systemic symptoms, perhaps both due to the myriad of side effects experienced with steroid treatment although this was not specifically evaluated. Also interestingly, worse QOL was seen in the social wellbeing, systemic and bowel symptoms categories in current/ex-smokers. As our number of current smokers was low (n=3) necessitating combination with the ex-smoking group, this group should be thought of overall, as an ex-smoking group. An association with former cigarette use and worse social wellbeing is a novel finding. Our smoking and QOL correlations warrant further investigation in larger groups in which the ex and current smokers can be studied separately.

### Limitations

This study has a several limitations. A selection bias is inherent to the study due to the inclusion of patients who chose to respond to the survey and thus could potentially could be more or less satisfied with their IPAA. We chose to score patients individual responses above or below the mean of all respondents in order to address this potential bias. The questionnaire did not contain questions about extra intestinal manifestations with the exception of PSC. Extra intestinal manifestations have been associated with worse QOL in prior studies [42]. Similarly, this study does not address other factors suggested to be associated with altered bowel symptoms such as pouch flora and diet [43,44], and certain specific factors associated with QOL such as social support in the form of membership in a support group, married *vs* single status [15] and patient personality. For two reasons, 1) in order to keep the survey as straightforward and short as possible, and 2) to capture patients suffering from chronic or acute pouchitis which may confound QOL results, antibiotic and steroid use was only evaluated in a 'now, ever or never' fashion. Number of courses and doses were not evaluated nor was QOL before the pouch. We also acknowledge the limitation of including patients with a short pouch duration. However, there was no difference between these patients and patients with longer pouch duration in any QOL comparison. In total, 9 patients out of the 142 had a pouch duration less than 2 years. Only 1 had a 6 month pouch duration, the remaining 8 had durations ≥ 1 year but < 2 years.

## Conclusion

Oftentimes the emotional and social disability associated with IPAA is overlooked. Previous studies have focused on pouchitis and other pouch-related symptoms that are associated with poor QOL that are only present postoperatively and therefore cannot be used to identify patients who will not be satisfied postoperatively. The above study demonstrates variables, such as urgent colectomy, female gender and smoking status as well as genetic determinants in the form of *POU5F1* and *TNSF15* SNPs that can be potentially utilized preoperatively to identify IPAA candidates who are at risk for poor quality of life postoperatively in several areas including emotional wellbeing and severe bowel symptoms.

## References

1. Parks AG, Nicholls RJ (1978) Proctocolectomy without ileostomy for ulcerative colitis. Br Med J; 2: 85-88.
2. Seidel SA, Peach SE, Newman M, Sharp KW (1999) Ileoanal pouch procedures: clinical outcomes and quality-of-life assessment. Am Surg; 65: 40-46.
3. Delaney CP, Fazio VW, Remzi FH, Hammel J, Church JM, et al. (2003) Prospective, age-related analysis of surgical results, functional outcome, and quality of life after ileal pouch-anal anastomosis. Ann Surg; 238: 221-228.
4. Fazio VW, Ziv Y, Church JM, Oakley JR, Lavery IC, et al. (1995) Ileal pouch-anal anastomoses complications and function in 1005 patients. Ann Surg; 222: 120-127.
5. Fazio VW, O'Riordain MG, Lavery IC, Church JM, Lau P, et al. (1999) Long-term functional outcome and quality of life after stapled restorative proctocolectomy. Ann Surg; 230: 575-584.
6. Thirlby RC, Sobrino MA, Randall JB. The long-term benefit of surgery on health-related quality of life in patients with inflammatory bowel disease. Arch Surg 2001; 136: 521-527.
7. Carmon E, Keidar A, Ravid A, Goldman G, Rabau M, et al. (2003) The correlation between quality of life and functional outcome in ulcerative colitis patients after proctocolectomy ileal pouch anal anastomosis. Colorectal Dis; 5: 228-232.
8. Robb B, Pritts T, Gang G, Warner B, Seeskin C, et al. (2002) Quality of life in patients undergoing ileal pouch-anal anastomosis at the University of Cincinnati. Am J Surg; 183: 353-360.
9. Berndtsson IE, Carlsson EK, Persson EI, Lindholm EA. (2011) Long-term adjustment to living with an ileal pouch-anal anastomosis. Dis Colon Rectum; 54: 193-199.
10. Casati J, Toner BB (2000) Psychosocial aspects of inflammatory bowel disease. Biomed Pharmacother; 54: 388-393.
11. Drossman DA, Leserman J, Li ZM, Mitchell CM, Zagami EA, et al. (1991) The rating form of IBD patient concerns: a new measure of health status. Psychosom Med; 53: 701-712.
12. Irvine EJ, (2008) Quality of life of patients with ulcerative colitis: past, present, and future. Inflamm Bowel Dis;14: 554-565.
13. Amoli MM, Carthy D, Platt H, Ollier WE (2008) EBV Immortalization of human B Lymphocytes separated from small volumes of cryo-preserved whole blood. Int J Epidemiol. 1: 41-45.
14. Guyatt G, Mitchell A, Irvine EJ, Singer J, Williams N, et al. (1989) A new measure of health status for clinical trials in inflammatory bowel disease. Gastroenterology 1989; 96: 804-810.

15. Oliveira S, Zaltman C, Elia C, Vargens R, Leal A, et al. Quality-of-life measurement in patients with inflammatory bowel disease receiving social support. Inflamm Bowel Dis 2007;13: 470-474
16. Han SW, Gregory W, Nylander D, Tanner A, Trewby P, et al. (2000) The SIBDQ: further validation in ulcerative colitis patients. Am J Gastroenterol; 95: 145-151.
17. McLeod RS, Baxter NN (1998) Quality of life of patients with inflammatory bowel disease after surgery. World J Surg; 22: 375-381.
18. Hauser W, Dietz N, Grandt D, Steder-Neukamm U, Janke KH, et al. (2004) Validation of the inflammatory bowel disease questionnaire IBDQ-D, German version, for patients with ileal pouch anal anastomosis for ulcerative colitis. Z Gastroenterol; 42: 131-139.
19. Lichtenstein GR, Cohen R, Yamashita B, Diamond RH (2006) Quality of life after proctocolectomy with ileoanal anastomosis for patients with ulcerative colitis. J Clin Gastroenterol; 40: 669-677.
20. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis; 40: 373-383.
21. Dindo D, Demartines N, Clavien PA Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg; 240: 205-213.
22. Connelly TM, Berg AS, Harris LR, Brinton DL, Hegarty JP, et al. (2014) Ulcerative colitis neoplasia is not associated with common inflammatory bowel disease single nucleotide polymorphisms.Surgery;156: 253-262.
23. Kiely JM, Fazio VW, Remzi FH, Shen B, Kiran RP, et al. (2012) Pelvic sepsis after IPAA adversely affects function of the pouch and quality of life. Dis Colon Rectum; 55: 387-392.
24. Koerdt S, Jehle EC, Kreis ME, Kasparek MS (2014) Quality of life after proctocolectomy and ileal pouch-anal anastomosis in patients with ulcerative colitis. Int J Colorectal Dis; 29: 545-554.
25. Brandsborg S, Nicholls RJ, Mortensen LS, Laurberg S (2013) Restorative proctocolectomy for ulcerative colitis: development and validation of a new scoring system for pouch dysfunction and quality of life. Colorectal Dis; 15: 719-725.
26. Lovegrove RE, Fazio VW, Remzi FH, Tilney HS, Nicholls RJ, et al. (2010) Development of a pouch functional score following restorative proctocolectomy. Br J Surg; 97: 945-951.
27. Andersson T, Lunde OC, Johnson E, Moum T, Nesbakken A et al. (2011) Long-term functional outcome and quality of life after restorative proctocolectomy with ileo-anal anastomosis for colitis. Colorectal Dis;13: 431-437.
28. Fazio VW, Kiran RP, Remzi FH, Coffey JC, Heneghan HM, et al. (2013) Ileal pouch anal anastomosis: analysis of outcome and quality of life in 3707 patients. Ann Surg; 257: 679-685.
29. Chapman JR, Larson DW, Wolff BG, Dozois EJ, Cima RR, et al. (2005) Ileal pouch-anal anastomosis: does age at the time of surgery affect outcome? Arch Surg; 140: 534-540.
30. El Demellawy D, El Hallani S, de Nanassy J, Lee JY, Chan E, et al. (2016) Value of histopathology for predicting the post-operative complications of ileo-anal anastomosis (J-pouch) procedure in children with refractory ulcerative colitis. Pathology; 48: 330-335.
31. Sehgal R, Berg A, Polinski JI, Hegarty JP, Lin Z, et al. (2012) Genetic risk profiling and gene signature modeling to predict risk of complications after IPAA. Dis Colon Rectum; 55: 239-248.
32. Kotani H, Masuda K, Tamagawa-Mineoka R, Nomiyama T, Soga F, et al. (2012) Increasedplasma LIGHT levels in patients with atopic dermatitis. Clin Exp Immunol; 168: 318-324.
33. Granger SW, Rickert S (2003) LIGHT-HVEM signaling and the regulation of T cell-mediated immunity. Cytokine Growth Factor Rev; 14: 289-296.
34. Petreaca ML, Yao M, Ware C, Martins-Green MM (2008) Vascular endothelial growth factor promotes macrophage apoptosis through stimulation of tumor necrosis factor superfamily member 14 (TNFSF14/ LIGHT). Wound Repair Regen; 16: 602-614.
35. Ware CF, Sedy JR (2011) TNF Superfamily Networks: bidirectional and interference pathways of the herpesvirus entry mediator (TNFSF14). Curr Opin Immunol; 23: 627-631.
36. Steinberg MW, Turovskaya O, Shaikh RB, Kim G, McCole DF, et al. (2008) A crucial role for HVEM and BTLA in preventing intestinal inflammation. J Exp Med; 205: 1463-1476.
37. Edwards TL, Shrubsole MJ, Cai Q, Li G, Dai Q, et al. (2013) Genome-wide association study identifies possible genetic risk factors for colorectal adenomas. Cancer Epidemiol Biomarkers Prev; 22: 1219-1226.
38. Steingart RA, Heldenberg E, Pinhasov A, Brenneman DE, Fridkin M, et al. (2002) A vasoactive intestinal peptide receptor analog alters the expression of homeobox genes. Life Sci; 71: 2543-2552.
39. Hochedlinger K, Yamada Y, Beard C, Jaenisch R (2005) Ectopic expression of Oct-4 blocks progenitor-cell differentiation and causes dysplasia in epithelial tissues. Cell; 121: 465-477.
40. Yasuda H, Tanaka K, Okita Y, Araki T, Saigusa S, et al. (2011) CD133, OCT4, and NANOG in ulcerative colitis-associated colorectal cancer. Oncol Lett; 2: 1065-1071.
41. Pavlides M, Cleland J, Rahman M, Christian A, Doyle J, et al. (2014) Outcomes after ileal pouch anal anastomosis in patients with primary sclerosing cholangitis. J Crohns Colitis; 8: 662-670.
42. Hauser W, Dietz N, Steder-Neukamm U, Janke KH, Stallmach A, et al. (2004) Biopsychosocial determinants of health-related quality of life after ileal pouch anal anastomosis for ulcerative colitis. Inflamm Bowel Dis; 10: 399-407.
43. Mimura T, Rizzello F, Helwig U, Poggioli G, Schreiber S, et al (2004) Once daily high dose probiotic therapy (VSL#3) for maintaining remission in recurrent or refractory pouchitis. Gut; 53: 108-114.
44. Lim M, Sagar P, Finan P, Burke D, Schuster H, et al. (2006) Dysbiosis and pouchitis. Br J Surg; 93: 1325-1334.