# The Effect of Liver Transplantation for Primary Sclerosing Cholangitis on Disease Activity in Patients with Inflammatory Bowel Disease

Mahmoud Mosli, MD, Kristopher Croome, MD, MS, Karim Qumosani, MD, Bandar Al-judaibi, MD, Melanie Beaton, MD, Paul Marotta, MD, and Natasha Chandok, MD, MPH

Dr. Mosli, Dr. Qumosani, and Dr. Al-judaibi are affiliated with the Department of Medicine of the Multi-Organ Transplant Unit of the London Health Sciences Centre of the University of Western Ontario in London, Ontario, Canada, where Dr. Beaton and Dr. Chandok are Assistant Professors of Medicine and Dr. Marotta is an Associate Professor of Medicine. Dr. Croome is a Transplant Hepatology Fellow in the Department of Surgery of the Multi-Organ Transplant Unit. Dr. Mosli is also affiliated with the Department of Medicine of King Abdulaziz University in Jeddah, Saudi Arabia. Dr. Qumosani is also affiliated with the Department of Medicine of King Fahad University Hospital of the University of Dammam in Dammam, Saudi Arabia. Dr. Al-judaibi is also affiliated with the Department of Medicine of King Khalid University Hospital of the King Saud University in Riyadh, Saudi Arabia.

Address correspondence to:
Dr. Natasha Chandok
Division of Gastroenterology
University of Western Ontario
339 Windermere Road
London, Ontario, Canada N6A5A5;
Tel: 519-663-3002;
Fax: 519-663-3858;
E-mail: dr.n.chandok@gmail.com

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**Abstract:** Immunosuppressive therapies are indicated following liver transplantation (LT) to prevent graft loss through rejection, and these same agents also may have a role in the management of inflammatory bowel disease (IBD). The aims of this study were to examine the effects of immunosuppression following LT on IBD activity and to identify markers of IBD control post-LT in patients with IBD who underwent LT for primary sclerosing cholangitis (PSC). A retrospective analysis of all adult patients with a pre-LT diagnosis of IBD who underwent LT for PSC over a 15-year period was performed. The primary outcome was IBD activity based on symptomatology and endoscopic assessment. Secondary outcomes included recipient mortality and post-LT development of colorectal cancer or small bowel lymphoma. A total of 105 patients underwent LT for PSC, and IBD was diagnosed in 27 (26%) pre-LT. Patients were followed for a mean of 88.5 months. Fourteen (52%) patients had stable IBD, 6 (22%) had worsening disease, and 7 (26%) had clinical improvement after LT. Colorectal cancer developed in 2 (7%) patients, and small bowel lymphoma developed in 1 (4%) patient. The absence of additional maintenance therapy for IBD was found to be associated with good outcome for IBD control. The use of either infliximab (Remicade, Janssen Biotech) or corticosteroids to control IBD post-LT was associated with poor outcome. Most patients with PSC and IBD had a stable course of IBD post-LT. The need for infliximab or additional or prolonged corticosteroids after LT appears to be a surrogate marker of aggressive disease.

Primary sclerosing cholangitis (PSC) is a chronic idiopathic inflammatory disorder involving the intra- and extrahepatic biliary ducts whereby biliary cirrhosis and portal hypertension lead to liver-related death in nearly half of affected patients.[1] Patients with PSC have a higher risk of development of certain

malignancies, including cholangiocarcinoma[2] and, in the presence of inflammatory bowel disease (IBD), colorectal cancer (CRC).[3] The only proven treatment for advanced PSC that offers a survival benefit is liver transplantation (LT).[4,5]

Following LT, patients receive immunosuppressant agents, typically as a triple-drug combination of a calcineurin inhibitor, an antimetabolite, and a tapering corticosteroid to prevent graft rejection. To a large extent, immunosuppression regimens in the LT recipient are nonstandardized, and there is broad practice variability and limited prospective data on which to extract evidence-based guidelines. Generally speaking, as the liver is a tolerogenic organ, recipients require relatively little immunosuppression compared with that needed by other solid-organ or multi-organ transplant recipients.[6] In the present era of LT, many transplantologists aim for corticosteroid-free immunosuppression, particularly beyond 3 months when the risk of acute cellular rejection diminishes.[7-9] In the past 2 decades, most LT recipients have received tacrolimus alone or tacrolimus in combination with mycophenolate mofetil (MMF) for long-term immunosuppression. These agents are used in lieu of cyclosporine and azathioprine combinations because of their improved potency and adverse effect profiles.[10]

The PSC/IBD overlap is common, with some population-based studies reporting PSC prevalence to be 2.4–4.0% in patients with ulcerative colitis (UC) and 1.4–3.4% in patients with Crohn's disease (CD). Conversely, 70–80% of patients with PSC have underlying IBD.[11-14] As an immune-mediated disease, IBD may respond to immunosuppressants received after LT. It is well established that the PSC/IBD phenotype is a unique form of IBD.[15-18] UC in patients with PSC is usually associated with extensive colitis, backwash ileitis, rectal sparing, a quiescent disease course, recurrent pouchitis following subtotal colectomy, and higher risk of CRC.[17,19,20] In contrast, there is some discrepancy in the literature on the strength of the association between PSC and CD. For instance, Rasmussen and colleagues found that, in a series of 262 patients with CD, just 10% had overlapping PSC.[12] However, a recent Canadian population-based study reported an equal risk of development of PSC in patients with UC and CD.[21] This latter observation has not been replicated in other epidemiologic studies.

Despite the strong associations between PSC and IBD to date, there are limited observational data on the natural history of IBD after LT for PSC. The standard medical treatment for colonic IBD includes 5-aminosalicylic acid (5-ASA), corticosteroids, and antimetabolites (ie, azathioprine). Given that some of these categories of medications are used following LT, it is a reasonable hypothesis that antirejection drugs could have an unintended therapeutic effect on IBD. However, data on this subject are conflicting and limited.[22] For instance, in 1991, a survey of 22 patients with prior LT for PSC found that 92% of respondents reported a stable course.[23] Comparable results were reported by Miki and colleagues, in which poor control of IBD was reported in 9 (35%) of 26 patients who received LT for PSC.[3] Similarly, Befeler and colleagues reported that 49% of patients with IBD had a quiescent course post-LT for PSC.[24] In contrast, a series from Royal Free Hospital estimated that an aggressive course of IBD post-LT in roughly half of recipients with PSC and UC overlap.[25] Likewise, a Dutch study reported a worsened IBD course in the majority of LT recipients with a history of PSC/UC overlap and also demonstrated a 28% malignancy rate post-LT.[26] Ho and colleagues also concluded that IBD follows an aggressive clinical course post-LT for PSC with more relapses, corticosteroid dependency, and a 19% rate of malignancy.[27] The observational studies on IBD post-LT are universally small, single-centered, and retrospective in design. As such, additional observational data may be useful in clarifying the effect of immunosuppression for prevention of rejection in patients with IBD who undergo LT for PSC.

The principal objective of this study was to determine the effect of immunosuppression on the post-LT course of IBD. The secondary objective was to identify predictors of IBD control among patients with a history of PSC/IBD overlap and primary LT.

## Methods

### *Patient Population*

Using the Liver Transplant Database in the Multi-Organ Transplant Unit of the London Health Sciences Centre at the University of Western Ontario, all patients age 18 years or older who underwent primary LT between January 1997 and January 2012 for PSC were identified. Patients with a pre-LT diagnosis of IBD were isolated by manually reviewing the organ transplant archives. Patients with a diagnosis of IBD made post-LT were excluded.

### *Data Collection*

Following approval by the Institutional Review Board at the University of Western Ontario, baseline clinical and demographic data were collected on each patient using hospital records. Verification of the diagnosis of IBD was performed by review of endoscopy and pathology reports. As part of the transplant assessment protocol, all patients scheduled for LT at the university's Multi-Organ Transplant Unit receive a screening colonoscopy within 1 year of transplantation to rule out CRC. All colonoscopy and pathology reports of patients entered into the study were reviewed. The medical therapies used for IBD were recorded. Disease activity was classified based on a preset

**Table 1.** Preset Definitions Used to Categorize Patients with IBD Based on Disease Activity

| Disease control | Time frame | Definition |
|---|---|---|
| **Pre-LT** | | |
| Active | 1 year pre-LT | Use of corticosteroids for symptoms of active IBD |
| | 3 months pre-LT | Symptoms of active disease |
| Stable | 1 year pre-LT | No corticosteroid use for symptoms of active IBD |
| | 3 months pre-LT | Absence of symptoms of active disease |
| **Post-LT** | | |
| Active | Any time post-LT | Symptoms of active disease confirmed by both endoscopic and pathologic evidence of disease activity and/or the need for corticosteroids for disease control and/or the addition of another therapeutic agent or an increase in the dose of an agent for disease control |
| Stable | 1 year post-LT | No corticosteroid use for symptoms of active IBD |
| | 3 months post-LT | Absence of symptoms of active disease |

IBD=inflammatory bowel disease; LT=liver transplantation.

scoring system that mirrors validated scoring systems and captures symptoms and histology (Table 1).

Active disease was defined as symptoms compatible with IBD within 3 months of LT confirmed by any evidence of active disease detected endoscopically or the need for systemic corticosteroids specifically for IBD control within 1 year of LT. Active post-LT disease was defined as symptoms compatible with IBD confirmed by both endoscopic and pathologic evaluation and/or the need for systemic corticosteroids for disease control and/or the addition of another therapeutic agent or an increase in the dose of a therapeutic agent being used for disease control. Stable disease was defined as having a 3-month, symptom-free period with a 1-year, steroid-free follow-up.

All patients received regular follow-up after LT. Follow-up intervals were dictated by overall clinical status, and in cases in which patients lived remotely, follow-up notes from their primary providers were obtained routinely and reviewed. The need for colectomy and the development of both CRC and small bowel lymphoma were recorded using patient records. Death certificates, autopsy reports, and/or patient charts were reviewed to identify cause of death where applicable. In patients who underwent multiple LTs, the first LT was used as an index for comparing IBD disease activity before and after LT. Patients whose disease activity worsened after LT were compared with those with stable or improved disease activity to identify predictors of worsening activity. The use of corticosteroids for IBD control beyond what is expected for graft preservation was considered as active disease. Although we acknowledge that colitis flares can certainly occur beyond 3 months after LT, it was decided, a priori, that an assessment at 3 months would minimize any loss to follow-up, as all LT recipients receive a clinical follow-up visit at this juncture.

### *Statistical Analysis*

Differences between groups were analyzed using the unpaired t-test for continuous variables and by the Chi test or continuity correction method for categorical variables. All statistical tests were 2-sided, and differences were considered significant when $P<.05$. Statistical analyses were performed using STATA version 10.0 software (STATA Corp., College Station, Texas).

### *Outcome Measures*

The primary endpoint was IBD disease activity post-LT. This was classified as stable, improved, or worsened depending on the presence or absence of change in disease activity before and after LT, as per previously defined criteria. Secondary endpoints included rates of post-LT colectomy, CRC, and small bowel lymphoma.

## Results

A total of 979 patients underwent 1,039 LTs between January 1997 and January 2012. LTs for PSC were performed in 105 (10%) patients. Of these 105 patients, 28 (27%) had concomitant IBD (17 cases of UC and 11 cases of colonic CD). One patient received a diagnosis of de novo CD post-LT and was, therefore, excluded from the analysis. The diagnosis changed post-LT from UC to CD in 2 patients. The majority of patients were men (76%). The mean age at the time of LT was 44.7 years (standard deviation [SD], 13.2; range, 11–65). The mean length of follow-up post-LT was 88.5 months (SD, 59.1; range, 13–239).

**Table 2.** Baseline Characteristics of the Study Population

| | Ulcerative colitis (n=17) | | Crohn's disease (n=10) | |
|---|---|---|---|---|
| | Males (n=13) | Females (n=4) | Males (n=7) | Females (n=3) |
| Mean age at LT, years | 49.15 (SD, 13.41; range, 11–65) | 42.75 (SD, 8.77; range, 30–46) | 36.86 (SD, 13.87; range, 16–51) | 46 (SD, 8.66; range, 36–51) |
| Mean time between PSC and IBD diagnosis, years | 9.76 (SD, 12.94; range, 1–37) | 13.25 (SD, 6.99; range, 5–20) | 10.28 (SD, 9.49; range, 0–28) | 10 (SD, 13; range, 2–25) |
| Improved/stable IBD post-LT, n | 11 | 4 | 5 | 1 |
| Worse IBD post-LT, n | 2 | 0 | 2 | 2 |

IBD=inflammatory bowel disease; LT=liver transplantation; PSC=primary sclerosing cholangitis; SD=standard deviation.

The majority of patients were maintained on MMF and tacrolimus post-LT (19/27, 70%). Fourteen (52%) patients had stable disease post-LT with no change in IBD control between pre- and post-LT. IBD worsened in 6 (22%) patients post-LT, requiring corticosteroid therapy, dose escalation of medications for IBD, or the addition of new medications for better control of IBD. Seven (26%) patients showed clinical improvement in IBD post-LT (Table 2). Four patients had a pelvic ileo-anal pouch constructed pre-LT. Two of these patients had stable disease post-LT, and 2 had worsening of disease with recurrent antibiotic-refractory pouchitis. No patients needed colectomy post-LT for uncontrolled IBD. Recurrent PSC in the hepatic graft developed in 3 (11%) patients. CRC requiring colectomy during follow-up post-LT developed in 2 patients. One patient presented with bowel obstruction during follow-up and received a diagnosis of small bowel post-transplant lymphoma. One patient died during follow-up from chronic rejection of the hepatic allograft.

Analysis revealed that being off any additional maintenance therapy apart from the antirejection immunosuppression regimen was associated with stable or improved disease post-LT ($P$=.033). Worsening of IBD control post-LT was associated with the use of infliximab (Remicade, Janssen Biotech; $P$=.006) or additional corticosteroids ($P$=.006) to control IBD symptoms post-LT. None of the patients requiring corticosteroids or infliximab post-LT for IBD control had active disease pre-LT. There was a trend toward but no statistical significance in predicting good outcome with the use of 5-ASA as maintenance therapy before LT ($P$=.081) or the use of cyclosporine alone or cyclosporine/MMF post-LT ($P$=.056). Additionally, there was no statistical significance in predicting poor outcome with the use of combination cyclosporine and infliximab as a maintenance regimen to control IBD post-LT ($P$=.056; Table 3). Furthermore, a comparison made between patients with stable or improved IBD post-LT and patients with worse IBD post-LT depending on the time of diagnosis of PSC or IBD, whichever occurred first, did not yield any statistically significant results ($P$=.23 for time to diagnosis of IBD on t-test and $P$=.239 on univariate logistic regression; $P$=.516 for time to diagnosis of PSC on t-test and $P$=.503 on univariate logistic regression).

## Discussion

The results of this study suggest that, for most patients, IBD follows a benign course following LT for PSC, and less than one third of patients had more aggressive disease after LT. As discussed, previous retrospective studies have shown conflicting data on the natural history of IBD in patients undergoing LT for PSC (Table 4). An analysis of the published literature suggests that maintenance immunosuppressive regimens, consisting of a combination of prednisone, cyclosporine, and azathioprine as described in older studies, were associated with improvement in UC following LT in the majority of recipients,[24] but the overall poor quality of evidence in the published literature prohibits definitive confirmation of the superiority of these regimens. A recently published article by Navaneethan and colleagues reported that a large series of patients with UC who underwent LT for PSC have a predominantly quiescent disease course post-LT with immunosuppressive regimens very similar to those reported in our study.[28]

It is reasonable to assume that standard immunosuppression post-LT may be sufficient to maintain remission in patients with IBD. This hypothesis would arise from our knowledge of the molecular basis of immunosuppression to prevent graft rejection and control IBD, where T-cell inhibition and subsequent inflammatory cytokine suppression is targeted in both instances.[29,30] Most agents used for post-LT immunosuppression have been extensively studied in IBD for both induction and maintenance of remission. The majority of these agents have been found to be effective in inducing, rather than maintaining, remission.[31] Corticosteroids, although key in controlling inflammation and effective in induction of remission in patients with IBD, are typically avoided

**Table 3.** Comparison Between Patients with IBD Who Had Stable/Improved Symptoms and Those with Worse Symptoms Post-LT

| Association | Stable/better post-LT (n=21) | Worse post-LT (n=6) | *P*-value |
|---|---|---|---|
| **Sex** | | | |
| Males (n=20) | 16 | 4 | .63 |
| Females (n=7) | 5 | 2 | .63 |
| **Diagnosis** | | | |
| UC (n=17) | 15 | 2 | .08 |
| CD (n=10) | 6 | 4 | .08 |
| **Location** | | | |
| Left-sided | 2 | 0 | .43 |
| Pancolitis | 16 | 4 | .63 |
| Pouch | 2 | 2 | .14 |
| Terminal-ileum | 1 | 0 | .58 |
| **Pre-LT IBD** | | | |
| Inactive | 13 | 5 | .32 |
| Active | 8 | 1 | .32 |
| **Pre-LT maintenance therapy** | | | |
| None | 10 | 4 | .41 |
| 5-ASA | 12 | 1 | .08 |
| Azathioprine/prednisone | 1 | 1 | .32 |
| Infliximab | 1 | 0 | .58 |
| **Post-LT immunosuppression** | | | |
| Tacrolimus/MMF | 15 | 4 | .82 |
| Tacrolimus/prednisone | 2 | 0 | .43 |
| Cyclosporine/MMF | 0 | 1 | .05 |
| Tacrolimus | 1 | 0 | .58 |
| Tacrolimus/cyclosporine | 1 | 0 | .58 |
| Cyclosporine | 0 | 1 | .05 |
| Tacrolimus/sirolimus | 1 | 0 | .58 |
| Tacrolimus/azathioprine/prednisone | 1 | 0 | .58 |
| **Post-LT maintenance therapy** | | | |
| None | 10 | 0 | .03 |
| 5-ASA | 10 | 1 | .17 |
| Corticosteroids | 0 | 2 | .006 |
| Azathioprine | 1 | 0 | .58 |
| Methotrexate | 0 | 0 | N/A |
| Infliximab | 0 | 2 | .006 |
| Infliximab/cyclosporine | 0 | 1 | .05 |
| **Outcome** | | | |
| Colorectal cancer | 1 | 1 | .32 |
| PTLD | 0 | 1 | .05 |
| Death | 0 | 1 | .05 |

5-ASA=5-aminosalicylic acid; CD=Crohn's disease; IBD=inflammatory bowel disease; LT=liver transplantation; MMF=mycophenolate mofetil; PTLD=post-transplant lymphoma; UC=ulcerative colitis.

**Table 4.** Previous Studies Examining the Course of IBD Post-LT

| Study | Cohort (period) | Patients (N) | Immunosuppressive regimen | IBD | Findings |
|---|---|---|---|---|---|
| Gavaler et al. 1991 | Pittsburgh, PA, USA (1982–1985) | 23 | Corticosteroid with cyclosporine | UC | 14/17 patients with active colitis pre-LT improved following LT; 0/23 deteriorated post-LT. |
| Shaked et al. 1992 | Los Angeles, CA, USA (1985–1990) | 24 | Corticosteroid with cyclosporine and azathioprine | UC | 16/24 patients improved or were unchanged post-LT. |
| Miki et al. 1995 | Birmingham, UK | 26 | Corticosteroid withdrawn after 3 months with either cyclosporine or tacrolimus and azathioprine | N/A | 9/26 patients had worsened control of colitis post-LT. |
| Papatheoridis et al. 1998 | London, UK (1989–1996) | 30 | Corticosteroid withdrawn after 3 months with either cyclosporine or tacrolimus and azathioprine | N/A | No patients improved, 15/30 worsened, and 10/30 patients with quiescent colitis worsened post-LT. |
| Befeler et al. 1998 | Chicago, IL, USA (1985–1996) | 23 | Corticosteroid with cyclosporine or tacrolimus with azathioprine | 19 UC 4 CD | 17/23 patients had quiescent colitis; 6/23 patients had minor flares that responded to 5-ASA agents. |
| Saldeen et al. 1999 | Gothenburg, Sweden (1986–1996) | 47 | N/A | 43 UC 3 CD 1 UDC | 65% of patients improved, and 8% worsened. |
| Graziadei et al. 1999 | Rochester, MN USA (1985–1996) | 82 | Corticosteroid withdrawn after 3 months with either cyclosporine or tacrolimus and azathioprine | 79 UC 3 CD | 9/82 patients had colectomy (5 due to active disease). |
| Van De Vrie et al. 2003 | Rotterdam, The Netherlands (1987–2000) | 18 | Corticosteroid withdrawn after 3 months with either cyclosporine or tacrolimus and azathioprine | 14 UC 4 CD | Unchanged overall, with 5/18 patients with active disease following LT. |
| Ho et al. 2005 | Edinburgh, Scotland, UK (1992–2003) | 20 | Corticosteroid withdrawn after 3 months with either cyclosporine or tacrolimus and azathioprine | UC | High number of relapse and corticosteroid requirement for active disease post-LT compared with pre-LT. |
| Villamil et al. 2008 | Buenos Aires, Argentina (1988–2006) | 24 | N/A | 23 UC 1 CD | 16/24 patients had quiescent colonic disease post-LT, 8/24 improved post-LT, and 3/24 had dysplasia and cancer. |
| Moncrief et al. 2010 | Edmonton, Alberta, Canada (1989–2006) | 42 | Cyclosporine or tacrolimus and azathioprine with or without a corticosteroid | 34 UC 6 CD | 67% were unchanged, 26.5% were worse, and 6.1% improved. |
| Joshi et al. 2011 | London, UK (1999–2009) | 74 | Prednisone and tacrolimus or prednisone and cyclosporine | 67 UC 6 CD 1 UDC | 58/74 patients had quiescent disease pre-LT, 16/74 had active disease pre-LT, 33/74 had flare post-LT, and 5/74 had cancer post-LT. |

5-ASA=5-aminosalicylic acid; CD=Crohn's disease; IBD=inflammatory bowel disease; LT=liver transplantation; UC=ulcerative colitis; UDC=undetermined colitis.

in long-term management because of their deleterious adverse effect profile.[32]

Cyclosporine, one of the earlier agents used for post-LT treatment, has been studied in IBD. There is weak evidence that cyclosporine is effective in inducing remission,[33,34] but it has not proven useful for maintenance of remission in IBD.[35] Azathioprine, on the other hand, is known to be an effective treatment for maintenance of

remission in IBD.[36,37] Even though some evidence supports the use of tacrolimus in induction of remission for both UC and fistulizing CD,[38,39] no studies support its use in maintaining remission in either disease. The same findings were reported with MMF, where there is some benefit in induction of remission in UC and CD but none for maintenance.[40,41] No randomized controlled trials examining the use of sirolimus in IBD exist, and, therefore, it is not clear what the overall role of this agent may be in maintaining remission in IBD.[42] Recent reports of an aggressive UC course post-LT in patients despite maximal immunosuppression raises the possibility that the aggressive course of UC post-LT may be caused by the shifting of immunosuppressant regimens to newer ones that have weaker evidence regarding their ability to maintain remission in IBD.[43,44] However, our results did not support this theory.

It is well known that patients with PSC and UC are at an increased risk for development of CRC after LT.[45-48] Previous studies have reported a nearly 4-fold increased risk of colon malignancy in patients with PSC and IBD post-LT compared with nontransplantation patients with UC with a similar duration of follow-up.[19,20] This is one of the major causes of mortality in patients with PSC and UC undergoing LT.[49] Therefore, it is recommended that patients with PSC/IBD undergo close colonic surveillance post-LT.[50] Alternatively, performing a colectomy with pelvic pouch ileo-anal anastomosis in patients with UC post-LT is also thought to be a safe option.[51] Our study population, notably, did not experience a large number of post-LT colonic cancers despite a long follow-up period.

The literature is not as ambiguous when it comes to the outcome of post-LT pelvic pouches, as it is almost uniformly thought that patients with UC who undergo proctocolectomy with pelvic ileal pouch-anal anastomosis before LT generally do well, with chronic antibiotic-refractory pouchitis developing in a subset of patients.[52-54] All 5 of the patients with a pelvic pouch in our study did well post-LT with no development of pouchitis.

Recurrent PSC has been reported to affect up to 20% of patients undergoing LT for PSC.[45,55] This is a major concern, as recurrence of PSC can alter long-term graft function and patient survival.[56] A PSC recurrence rate of 11% was noted in our series, but there was no correlation between PSC recurrence and aggressive IBD.

This study identified predictors of IBD outcome post-LT. Not requiring IBD maintenance therapy post-LT was found to be statistically significantly associated with a good outcome (stable or improved disease). This could be a reflection of previously controlled disease activity or a response to the standard immunosuppression regimen used to prevent graft rejection. Similarly, the only marker associated with poor IBD outcome—the use of either corticosteroids or infliximab post-LT to control IBD—probably represents a surrogate marker of aggressive disease. The small sample size of the present study should be considered while interpreting these results, as findings regarding corticosteroid or infliximab use post-LT could be a result of a type 1 statistical error.

The strengths of the study presented herein lay in close and lengthy follow-up and use of strict endoscopic and histologic criteria to define outcomes. This study, however, is limited by the retrospective nature of data collection in addition to a small sample size. Furthermore, we acknowledge the lack of standardization for assessment of IBD severity and the potential for interobserver variability in the reporting of colonoscopic or pathologic findings as potential limitations. Nevertheless, the present study offers a useful contribution to the growing knowledge on the natural history of post-LT IBD. Our findings suggest the need for prospective multicenter studies to better define the natural history of post-LT IBD and to identify more clinically relevant predictors of aggressive IBD.

In conclusion, our results suggest that the majority of patients with IBD and PSC undergoing LT have a stable disease course post-LT.

*The authors have no conflicts of interest to disclose.*

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