Non-hepatic Solid Organ Transplant in Patients with Inflammatory Bowel Disease: An ECCO CONFER Multicentre Case Series

Non-hepatic solid organ transplant in patients with inflammatory bowel disease: an ECCO CONFER Multicentre Case Series

Davide Giuseppe Ribaldone[1], Sophie Vieujean[2], Mette Julsgaard[3], Angelo Armandi[1], Fabiana Zingone[4], Edoardo Savarino[4], Fiorella Cañete[5], Annalisa Aratari[6], Nicola Imperatore[7], Laura Ramos[8], Rocio Plaza[9], Daniela Pugliese[10], Brigida Barberio[4], David Drobne[11, 12], María Chaparro[13]

[1] Department of Medical Sciences, Division of Gastroenterology, University of Turin, Turin, Italy

[2] Hepato-Gastroenterology and Digestive Oncology, University Hospital CHU of Liège, Liège, Belgium

[3] Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark

[4] Division of Gastroenterology, Department of Surgery Oncology and Gastroenterology DiSCOG, University of Padova, Padova, Italy

[5] IBD Unit. Hospital Universitari Germans Trias i Pujol, Badalona, Spain. Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, España

[6] IBD Unit, San Filippo Neri Hospital, Rome, Italy

[7] Gastroenterology and Endoscopy Unit, AORN Antonio Cardarelli of Naples, Naples, Italy

[8] Gastroenterology and Hepatology Department, Hospital Universitario de Canarias, Universidad de La Laguna, Tenerife, Spain

[9] Gastroenterology Department, Hospital Universitario Infanta Leonor, Vallecas, 28031 Madrid, Spain

[10] CEMAD, IBD CENTER, Unità Operativa Complessa di Medicina Interna e Gastroenterologia, Dipartimento di Scienze Mediche e Chirurgiche, Fondazione Policlinico Universitario 'A. Gemelli' IRCCS, Rome, Italy

[11] Department of Gastroenterology, University Medical Centre Ljubljana, Ljubljana, Slovenia

[12] Medical Faculty, University of Ljubljana, Ljubljana, Slovenia

[13] Servicio de Aparato Digestivo, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IIS-Princesa), Universidad Autónoma de Madrid (UAM), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain.

Short title: Solid organ transplant and IBD

Abbreviations:

CD = Crohn’s disease

IBD = inflammatory bowel diseases

IgA = immunoglobulin A

IQR = interquartile range

SD = standard deviation

UC = ulcerative colitis

Author contributions: Davide Giuseppe Ribaldone wrote the protocol of the study and Maria Chaparro and Angelo Armandi revised it. Davide Giuseppe Ribaldone, Sophie Vieujean, Mette Julsgaard, Fabiana Zingone, Edoardo Savarino, Fiorella Cañete, Annalisa Aratari, Nicola Imperatore, Laura Ramos, Rocio Plaza, Daniela Pugliese, Brigida Barberio, David Drobne, María Chaparro collected patient data. Davide Giuseppe Ribaldone wrote the first version of the article which was firstly revised by Maria Chaparro and Angelo Armandi and later by the other authors. Davide Giuseppe Ribaldone did the statistical analysis.

Davide Giuseppe Ribaldone is the guarantors of the article.

Data availability: Data are available upon reasoned request.

Correspondence: Davide Giuseppe Ribaldone, Department of Medical Sciences, Division of Gastroenterology, University of Turin, Turin, Italy, davidegiuseppe.ribaldone@unito.it

Abstract

Background and Aims: Solid organ transplantation, with the exception of liver, has rarely been reported in patients affected by inflammatory bowel diseases (IBD).

Methods: This is an ECCO-CONFER project collecting cases of solid organ transplants (with the exclusion of liver) that were performed in IBD patients. We evaluated the change in the IBD therapy, need for bowel resection due to medically refractory IBD, or need for hospitalization due to IBD relapse ("severe IBD course") before and after transplantation.

Results: Thirty-four organ transplantations (28 kidney, five heart, one lung) in 33 IBD patients were collected (67% male; 55% Crohn's disease, mean age 53 ± 16 years). The median follow-up was 4.3 years (IQR 3.2 – 10.7). Twenty-nine patients (87.9%) were treated with tacrolimus, 25 (76%) with systemic steroids, 22 (67%) with mycophenolate mofetil, 11 (33%) with everolimus, six with cyclosporine (18%). One patient was treated with infliximab, two patients with adalimumab, two patients with vedolizumab, one patient with ustekinumab. Overall, a severe IBD course was observed in three (9.3%) patients before transplantation and in four (11.7%) in the post-transplant setting (p = 0.26). Three cases of cancer (excluding skin non-melanoma) (9.1%) were recorded in post-transplantation period versus two in the pre-transplant (6.1%, p = 0.04).

Six patients (18.2%) died during the period of observation. No deaths were associated with IBD or complications of the transplant.

Conclusions: In IBD patients, solid organ transplantation does not seem to impact on the IBD severity. However, the risk of malignancy needs further investigation.

81 **Keywords:** infections; lymphoma; ulcerative colitis

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases (IBD). In about one third of the cases, IBD may be complicated by extra-intestinal manifestations, including primary sclerosing cholangitis, renal dysfunction, arterial ischaemic events, interstitial and granulomatous lung disease, or autoimmune pancreatitis.[1,2]

Because of the high occurrence of primary sclerosing cholangitis among IBD patients, most studies on solid organ transplantation in the setting of IBD refer to liver transplantation.[3,4]

The IBD therapy is often based on immunomodulatory drugs (including immunosuppressive or biological therapy), which requires a careful management of potential infectious or neoplastic diseases during follow up. The occurrence of an organ transplantation represents a further critical issue in this population, due to the additional immunosuppressive regimens for the prevention of graft rejection. For instance, incidence of extra-colonic tumours is higher in IBD patients undergoing liver transplantation.[3]

So far, limited data are available on the course of the underlying IBD following solid organ transplantation. A beneficial effect of the additional immunosuppressive therapy would be expected, considering the immune-mediated pathophysiology of IBD. However, several studies have provided discordant outcomes, potentially due to the diverse regimes adopted in the post-transplant setting.[5,6]

The aim of this European Crohn's and Colitis Organisation (ECCO) COllaborative Network For Exceptionally Rare case reports project (ECCO-CONFER) was to perform an observational study in order to evaluate the course of IBD before and after solid organ

transplantation with the exclusion of the liver. The assessment of the immunosuppressive regimens adopted after organ transplantation, the IBD therapy before and after transplantation, and the prevalence of target therapy in this population represented the objectives of this retrospective observational series. Additionally, the impact of the post-transplant immunosuppressive regimens on the IBD course, and the rate of infectious or tumour diseases were assessed.

Material And Methods

This was a retrospective observational multicentre study of IBD cases across Europe through the ECCO-CONFER.[7] The CONFER project was promoted by ECCO in order to detect and report rare IBD associations. The ECCO CONFER projects are promoted by ECCO to support individual investigators in the development of rare case series in the IBD Community. This promotion includes dissemination of a call for similar cases, as well as assessment of the feasibility of the cases by the ECCO CONFER Steering Committee. It does not include any financial support nor any input in the analysis or the publication of the data collected. ECCO, and/or any of its staff members, may not be held liable for any information published in good faith in the ECCO CONFER articles. Briefly, the CONFER methodology requires ECCO members to suggest and submit a topic which is worthy of investigation. The CONFER steering committee choses the best topic and a formal ECCO call is launched to gather all similar cases involved in the topic worldwide. The ECCO call to physicians is launched through announcements during the ECCO annual Congress and at national IBD meetings across Europe. In addition, the ECCO call for similar cases of the defined topic is shared through direct emails to all ECCO members and affiliated physicians, as well as on the ECCO website and through the ECCO eNews.

We included patients affected by IBD, which diagnosis was made according to the ECCO criteria[8], with a history of solid organ transplantation after IBD diagnosis. A minimum of one year -follow up after IBD diagnosis was required. Exclusion criteria were: liver or bone marrow transplantation, any transplantation performed before IBD diagnosis, and lack of clinical follow-up documentation.

In the pre-transplant period, the follow up started at the time of IBD diagnosis and ended at the time of transplantation. In the post-transplant period, the follow-up started at the time of transplantation, and ended at the last follow-up visit or death.

The outcomes of this study included: the changes in the IBD therapy; surgical complications of IBD (bowel resection for to medically refractory IBD, stenosing or penetrating complications); hospitalization for IBD relapse ("severe IBD course")[3] either before or after transplant. ~~The risk factors for either escalation of IBD medical therapy or the need for post-transplant surgery were studied and stratified according to: gender; smoking habit; clinical, biochemical, and endoscopic IBD activity at the time of transplantation; disease duration; age at diagnosis and at the time of transplantation; different immunosuppressive regimens adopted after liver transplantation.~~

Additionally, incidence rates of colonic dysplasia, colorectal cancer, solid tumours, and infectious diseases, were assessed before and after transplantation.

All data were collected and analysed anonymously and handled according to local regulations. The ECCO CONFER Cases project was centrally approved by the Institutional Review Board (IRB) of the Sheba Medical Center (Israel).

Statistical analysis

Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR) as needed and compared using Student's t-test or Mann-Whitney test, respectively. Categorical variables were expressed as proportions and compared by the Chi-squared test. The comparison of the primary outcome (the need for biologic therapy, bowel resection, or hospitalization for IBD flare) before and after

transplantation was performed using the Kaplan-Meier survival curve analysis. ~~The impact of potential risk factors on the outcomes was analysed by Cox proportional-hazards regression multivariate analysis.~~ A p-value less than 0.05 was considered statistically significant. All the statistical analyses were performed using MedCalc software, version 18.9.1 (MedCalc bvba, Ostend, Belgium).

Results

Study population

Thirty-four organs transplanted after IBD diagnosis in 33 patients (n = 22, 66.7%, males; n = 18, 54.5%, CD, n = 14, 42.4% UC, one, 3.0%, unclassified IBD, IBD-U) were collected from 12 referral centres in five different countries (Supplementary Table 1). A patient underwent kidney re-transplantation following rejection. The majority of cases (n = 29, 87.9%) were reported from academic tertiary centres.

Mean age at solid organ transplantation was 53.0 ± 15.6 years. The most frequently transplanted organ was the kidney (27 transplants, 81.8%, one re-transplantation), followed by the heart (four transplants, 12.2%), and the lung (one transplant, 3.0%); one patient underwent a combined heart and kidney transplant (3.0%). No cases of pancreas, bowel, or corneal transplantations were reported.

Patients underwent transplantation after a mean time of 18.4 ± 14.7 years from IBD diagnosis. The median follow-up after transplantation was 4.3 years (IQR 3.2 – 10.7). Clinical characteristics of the patients are reported in Table 1 and the causes of transplantation are shown in Supplementary Table 2.

Out of 33 patients, 10 (30.3%) had a history of at least one bowel resection for IBD prior to transplantation, while 16 patients (48%) had a history of at least one hospitalization due to IBD exacerbation prior to transplantation.

Transplantation outcome

Regarding the immunosuppressive therapy following solid organ transplantation, 29 patients (87.9%) were treated with tacrolimus, 25 (75.8%) with systemic steroids, 22 (66.7%) with mycophenolate mofetil, 11 (33.3%) with everolimus, six patients with cyclosporine (18.2%), three patients (9.1%) with thiopurines as anti-rejection therapy, and one patient (3.0%) with sirolimus.

Out of 33 patients, 7 (21.2%) experienced organ rejection: among the five cases of heart transplantation, one mild rejection (20%) was observed; among the 28 kidney transplantation cases, we reported two mild rejections (7.1%), and three severe rejections (10.7%) of which one undergoing re-transplantation due to plasma cell rejection; one mild rejection was observed in the lung transplantation case.

Six (18.2%) patients died at follow up; causes of death were: one cholangiocarcinoma, one complicated amyloidosis, one heart failure, one myocardial infection in patients with previous kidney transplantation, whereas in two patients the cause of death was unknown (one death in kidney and one death in heart transplantation, respectively).

Inflammatory bowel disease course before transplantation

A “severe IBD course” was observed in 9.3% of in the first 4.3 years before transplantation

Inflammatory bowel disease course after transplantation

After transplantation, six patients (18.2%) were hospitalized due to IBD relapse, and two patients (6.1%) underwent intestinal surgery due to worsened IBD activity: both not statistically different from the pre-transplant period (Logrank p = 0.11 and p = 0.32, respectively).

The cumulative probability of a “severe IBD course” was non different in the pre-transplantation and post-transplantation period (Logrank p = 0.26) (Figure 1): in particular a “severe IBD course” was observed in 11.7% of patients in the 4.3 years following post-transplantation. ~~The univariate analysis for the prediction of severe IBD course after transplantation is reported in Table 2. Due to the limited sample size, the multivariate analysis was not statistically feasible.~~

Considering the IBD biologic therapy, one patient (3.0%) was treated with infliximab (heart transplant), two patients (6.1%) with adalimumab (one heart transplant, one kidney transplant), two patients (6.1%) with vedolizumab (heart transplant), one patient (3.0%) with ustekinumab (heart transplant).

Tumours before transplantation

One case of indefinite dysplasia was recorded prior to transplantation, with no confirmation of colonic dysplasia at follow up post-transplant. No cases of colon cancer were recorded prior to the transplant.

In the pre-transplantation period, two cases of cancers (excluding non-melanoma skin cancers) were recoded (6.1%).

Tumours after transplantation

One case (3.0%) of low-grade colonic dysplasia was observed 10 years after heart transplantation in one UC patient treated with cyclosporine and everolimus. Additionally, one case of colonic cancer (3.0%) occurred after five years from kidney transplantation in one CD patient treated with steroids, cyclosporine, everolimus, mycophenolate mofetil and tacrolimus. None of these patients used biological therapy for IBD.

All cases of cancer occurrence after transplantation are reported in Table 2~~3~~. In particular, one case of vocal cord tumour (six years after transplantation), one case of cholangiocarcinoma (five years after transplantation), and one case of melanoma (one year after transplantation) were recorded (9.1%) (hazard ratio, H.R. = 10.0, 95% CI = 0.8 – 118.9, p = 0.04 compared with pre-transplantation period); none of these patients were treated with biologic therapy after transplantation.

No cases of lymphoma were recorded after transplantation, while one patient had a previous history of non-solid transplantation due to lymphoma with complete recovery.

Infections before transplantation

Twenty-eight infectious episodes occurred in the pre-transplantation period.

Infections before and after transplantation

Seventeen patients (51.5%) reported at least one episode of severe infection after transplantation (median time after transplantation = 2 years, IQR = 0 – 9.5 years). Overall, 29 severe infectious episodes occurred after transplantation (p = 0.90, compared to pre-transplantation period). The first occurrence of a severe infection after transplantation is shown in Table 34.

Discussion

With the exception of the liver, few data concerning solid organ transplantation in the IBD population are available. We have presented the first largest international multicenter study exploring the course of IBD after solid organ transplantation (mainly kidney, but also heart and lung transplantation) in a cohort of 33 patients across a median follow-up time of four years.

The main limitation of the current evidence in this field is the restriction to single centre or national cohorts, as well as small sample sizes that did not allow for subgroup analyses. A recent study conducted on patients undergoing kidney transplantation due to immunoglobulin A (IgA) nephropathy or polycystic kidney disease, reported a five-year post-transplant survival of 80.8% in individuals with IBD, compared to 96.8% of those without ($p = 0.001$).[9] All IBD patients, which were in a remission state before transplant, maintained remission without the need for additional medications. The IBD patients with mildly active disease which were under infliximab therapy, did not require any adjustments after the transplant. In addition, one patient undergoing adalimumab therapy for moderately active CD before the transplant, showed a clinical improvement after the transplant, hence no treatment adjustments were needed.[9] Another study of 1537 patients with IBD described the outcomes of six patients (five CD and one UC) undergoing kidney transplant[10] with an 84% survival rate at a median follow-up of 33 months. In this study, one patient developed papillary renal cell carcinoma in the transplanted kidney, but no graft rejections were reported. Additionally, a retrospective study examined 16 IBD patients under anti-TNFα therapy undergoing kidney transplant[11]. In this cohort, a significant proportion of serious infections (50% of patients) was reported. Another study

by Schnitzler's et al[10] described a 29 year old patient with CD undergoing heart transplantation for congestive heart failure due to ischaemic dilative cardiomyopathy. The patient was diagnosed with CD at the age of 22 and was treated with tacrolimus, mycophenolate mofetil, and steroids following heart transplantation; he was additionally treated with infliximab after the transplant, obtaining a successful remission of the IBD.

In the present study, we recorded only one kidney re-transplant and a four-year survival rate for kidney transplant of 96.4%. This data is comparable to that of the United Kingdom, where the graft survival rate among the general population is 94% after one year and 86% after five years following transplant. Patient survival rates were 97% and 88% after one year and five years, respectively.[12] In our study. the survival rate of the patients was 81.8% after 4.3 year, which is in line with previous studies.[9,10]

In our cohort, the majority of patients was treated with tacrolimus, followed by mycophenolate mofetil, and everolimus. None of these drugs has shown an association with the course of IBD after transplantation, despite patients treated with tacrolimus or everolimus showing a less aggressive course, as compared to those treated with mycophenolate mofetil.

Overall, we did not find a significant difference in the severity of IBD course before and after transplantation. This finding differs from previous studies, where tacrolimus-based treatment regimens were linked to a poor outcome in IBD patients undergoing solid organ transplant, with up to four-fold increased risk of IBD relapse following the transplant.[13–15]

For individuals with refractory, steroid-dependent, or fistulizing IBD, biological therapy has proven to be a beneficial treatment option. Only few studies including patients

undergoing post-transplant anti-TNF medications have been so far published.[9–11] Our study shows for the first time the data about post-transplant treatment with vedolizumab and/or ustekinumab: one patient experienced two non-fatal lung infections, but no cancer events were recorded.

In this cohort, no cases of lymphoma were recorded after transplantation. However, cancer incidence showed a higher trend in the post-transplant setting, when compared to the pre-transplant setting, but future studies are warranted to better investigate this topic. Gastroenterologists should be aware of the risk and emphasise a regular monitoring of patients with IBD following solid organ transplantation.

In the present study, the risk of serious infections is in line with previous findings by Garrouste and colleagues.[11] Furthermore, the risk of serious infections is similar between pre- and post-transplant setting. Of note, the rate of cytomegalovirus (CMV) infection in our population was lower than that in the general population following kidney transplantation (17.8%-63.2%).[16]

Our study has some limitations. Firstly, this is a retrospective case report data collection and it relied on voluntary submission of cases by physicians who responded to the ECCO calls and thus might be subjected to geographical and selection biases. Nonetheless, all eligible patients were rigorously screened. Secondly, due to the small sample size, robust conclusions on the association between IBD and transplant factors cannot be drawn. However, this is the largest and first multi-national study that directly compared IBD outcomes before and after solid organ transplantation. Furthermore, our population comprises real-life patients who are typically monitored in referral IBD centres, enhancing the validity of our findings. Notably, the disease course is highly unpredictable over the

317 years, making the comparison before and after the transplant less reliable. The long follow
318 up of observation may partially overcome these limitations.

319 In conclusion, in this large case series of IBD patients, we showed that solid organ
320 transplantation is not associated with a worsening of IBD course, despite a major
321 incidence of solid tumours may occur. We observed a medium-term survival rate of about
322 80%, which would enhance careful screening strategies. Future studies are needed to
323 explore the risk of cancer in IBD populations undergoing solid organ transplantation. A
324 larger sample size is needed to confirm our findings and to investigate the best
325 immunosuppressive treatment regimens in this population.

326

327 **Conflicts of Interest Statement**

328 Davide G. Ribaldone: None to declare.

329 Sophie Vieujean: None to declare.

330 Mette Julsgaard has received research grants for other investigator-driven studies from
331 Takeda, has received consultation fee from Ferring and Takeda, and has received
332 speaker's fees from MSD, Ferring, and Takeda.

333 Angelo Armandi: None to declare.

334 Fabiana Zingone: None to declare.

335 Edoardo V. Savarino: None to declare.

336 Fiorella Cañete: None to declare.

Annalisa Aratari: None to declare.

Nicola Imperatore: None to declare.

Laura Ramos: None to declare.

Rocio Plaza: None to declare.

Daniela Pugliese: None to declare.

Brigida Barberio: has served as speaker for Alfasigma, Janssen, Procise, Sofar, Takeda; has served as consultant for Doxapharma.

David Drobne: None to declare.

María Chaparro: Speaker, consultant or research or education funding from MSD, Abbvie, Hospira, Pfizer, Takeda, Janssen, Ferring, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, Biogen, Gilead, and Lilly.

Funding Statement

Note to declare.

References

1. Eliadou E., Moleiro J., Ribaldone D., Astegiano M., Rothfuss K., Taxonera C., et al. Interstitial and granulomatous lung disease in inflammatory bowel disease patients. *Journal of Crohns & Colitis* 2018;**12**:S308–S308.
2. Ribaldone DG., Pellicano R., Actis GC. The gut and the inflammatory bowel diseases inside-out: Extra-intestinal manifestations. *Minerva Gastroenterologica e Dietologica* 2019:309–18. Doi: 10.23736/S1121-421X.19.02577-7.
3. Ribaldone DG., Imperatore N., Le Grazie M., Furfaro F., Balestrieri P., De Blasio F., et al. Inflammatory bowel disease course in liver transplant versus non-liver transplant patients for primary sclerosing cholangitis: LIVIBD, an IG-IBD study. *Digestive and Liver Disease : Official Journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver* 2021;**53**(6):712–6. Doi: 10.1016/J.DLD.2020.09.011.
4. Barberio B., Massimi D., Cazzagon N., Zingone F., Ford AC., Savarino EV. Prevalence of Primary Sclerosing Cholangitis in Patients With Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. *Gastroenterology* 2021;**161**(6):1865–77. Doi: 10.1053/j.gastro.2021.08.032.
5. Vrus J., Jukić NB. Inflammatory Bowel Diseases in Renal Transplantat Recipients: A Case Series and Review of the Literature. *Prilozi (Makedonska Akademija Na Naukite i Umetnostite Oddelenie Za Medicinski Nauki)* 2022;**43**(1):57–63. Doi: 10.2478/PRILOZI-2022-0006.
6. Martínez Montiel M del P., Herce BC. Inflammatory bowel disease and solid organ transplantation. *Revista Espanola de Enfermedades Digestivas : Organo Oficial de La*

Sociedad Espanola de Patologia Digestiva 2021;**113**(1). Doi: 10.17235/REED.2020.7361/2020.

7. Katsanos KH., Domènech E., Rahier JF., Kopylov U., Fiorino G., Rogler G., et al. Making a Case for Case Reports: The ECCO-CONFER Viewpoint on Investigating Rare Events in a Medical World Reigned by Group-comparative Statistics. *Journal of Crohn's & Colitis* 2017;**11**(2):256–7. Doi: 10.1093/ECCO-JCC/JJW131.
8. Maaser C., Sturm A., Vavricka SR., Kucharzik T., Fiorino G., Annese V., et al. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. *Journal of Crohn's and Colitis* 2019;**13**(2):144–64. Doi: 10.1093/ecco-jcc/jjy113.
9. Grupper A., Schwartz D., Baruch R., Schwartz IF., Nakache R., Goykhman Y., et al. Kidney transplantation in patients with inflammatory bowel diseases (IBD): analysis of transplantation outcome and IBD activity. *Transplant International : Official Journal of the European Society for Organ Transplantation* 2019;**32**(7):730–8. Doi: 10.1111/TRI.13415.
10. Schnitzler F., Friedrich M., Stallhofer J., Schönermarck U., Fischereder M., Habicht A., et al. Solid Organ Transplantation in Patients with Inflammatory Bowel Diseases (IBD): Analysis of Transplantation Outcome and IBD Activity in a Large Single Center Cohort. *PloS One* 2015;**10**(8):e0135807. Doi: 10.1371/journal.pone.0135807.
11. Garrouste C., Anglicheau D., Kamar N., Bachelier C., Rivalan J., Pereira B., et al. Anti-TNFα therapy for chronic inflammatory disease in kidney transplant recipients: Clinical outcomes. *Medicine* 2016;**95**(41). Doi: 10.1097/MD.0000000000005108.

12. Aiyegbusi O., McGregor E., McManus SK., Stevens KI. Immunosuppression Therapy in Kidney Transplantation. *The Urologic Clinics of North America* 2022;**49**(2):345–60. Doi: 10.1016/J.UCL.2021.12.010.
13. Singh S., Loftus E V., Talwalkar JA. Inflammatory Bowel Disease after Liver Transplantation for Primary Sclerosing Cholangitis. *The American Journal of Gastroenterology* 2013;**108**(9):1417–25. Doi: 10.1038/ajg.2013.163.
14. Dvorchik I., Subotin M., Demetris AJ., Fung JJ., Starzl TE., Wieand S., et al. Effect of liver transplantation on inflammatory bowel disease in patients with primary sclerosing cholangitis. *Hepatology* 2002;**35**(2):380–4. Doi: 10.1053/jhep.2002.30695.
15. Verdonk RC., Dijkstra G., Haagsma EB., Shostrom VK., Van den Berg AP., Kleibeuker JH., et al. Inflammatory Bowel Disease After Liver Transplantation: Risk Factors for Recurrence and De Novo Disease. *American Journal of Transplantation* 2006;**6**(6):1422–9. Doi: 10.1111/j.1600-6143.2006.01333.x.
16. Pakfetrat M., Malekmakan L., Jafari N., Sayadi M. Survival Rate of Renal Transplant and Factors Affecting Renal Transplant Failure. *Experimental and Clinical Transplantation : Official Journal of the Middle East Society for Organ Transplantation* 2022;**20**(3):265–72. Doi: 10.6002/ECT.2021.0430.

Figure 1. Comparison of aggressive IBD course after and before transplantation

Table 1. Clinical characteristics of patients with inflammatory bowel diseases and solid organ (with the exception of liver) transplantation

Total patients, n	33
Age at IBD diagnosis	
Median years (IQR)	33.5 (21.8-40.0)
Age at transplant	
Mean years ± SD years	53.0 ± 15.6
Gender, n (%)	
Male	22 (66.7)
Ethnicity, n (%)	
Caucasian	31 (96.9)
Peruvian	1 (3.1)
N.A.	1
IBD type, n (%)	
CD	18 (54.5)
UC	14 (42.4)
IBD-U	1 (3.0)
Montreal classification, n (%)	
CD	
L1	5 (27.8)
L2	4 (22.2)
L3	8 (44.4)

L3 + L4	1 (5.6)	425
UC		426
E1	2 (14.3)	427
E2	7 (50.0)	428
E3	5 (35.7)	429
Perianal disease in CD		430
n/total (%)	6/18 (33.3)	431
Positive family history of IBD		432
n/total (%)	4/32 (12.5)	433
N.A.	1	434
Smoking habit		435
Current	6/30 (20)	436
Past	9/30 (30)	437
Never	15/30 (50%)	438
N.A.	3	439
Previous Drug Exposure, n (%)		440
Systemic steroids	21 (63.6)	441
Thiopurine	15 (45.5)	442
Methotrexate	3 (9.1)	443
Infliximab	8 (24.2)	444
Adalimumab	8 (24.2)	445
Vedolizumab	2 (6.1)	446

447 n, number; IBD, inflammatory bowel disease; IQR,

interquartile range; SD, standard deviation; IBD-U, unclassified IBD; CD, Crohn's disease; UC ulcerative colitis; L1, ileal; L2, colonic; L3, ileocolonic; L4, upper disease; E1, up to the rectum; E2, up to splenic flexure; E3, extensive colitis; N.A., not available

Table 2. Univariate analysis (predictors of "severe IBD course" after transplantation)

Factor	H.R.	p value
Male sex	5.78	0.11
IBD duration	1.001	0.64
Current smoker	0.92	0.94
Clinically active* IBD at transplant	0.74	0.78
Age at diagnosis	0.99	0.73
Age at transplantation	1.003	0.93
Crohn's disease	1.11	0.90
CRP at transplantation	1.01	0.71
Endoscopic activity** at transplantation	1.47	0.68
Tacrolimus	0.48	0.40
Mycophenolate mofetil	1.70	0.54
Cyclosporine	0.84	0.85
Everolimus	0.31	0.28
Thiopurine	1.06	0.96

H.R., hazard ratio; IBD, inflammatory bowel disease; CRP, C-reactive protein

* moderate or severe clinical activity according to HBI or pMAYO or systemic steroids in the last three months

** presence of ulcers

Table 23. Solid non-colorectal tumours after transplantation

Location	Total patients
Vocal cord	1
Skin (non-melanoma)	7
Melanoma	1
Bile ducts	1

Table 34. First serious infectious episode after transplantation

Location	Total patients
Blood (CMV)	2
Gastrointestinal tract	1
Lung	9
Upper respiratory tract	1
Skin	1
Urinary tract	3

CMV = cytomegalovirus