ORIGINAL ARTICLE

Kidney transplantation in patients with inflammatory bowel diseases (IBD): analysis of transplantation outcome and IBD activity

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SUMMARY

Inflammatory bowel diseases (IBD) is a systemic disorder with possible renal involvement, yet data regarding the outcome of kidney transplantation (KT) in those patients, and IBD course post KT, are scarce. In this retrospective analysis, we studied the outcome of 12 IBD kidney recipients (seven Crohn's disease, five ulcerative colitis; primary kidney disease was IgA nephropathy in five, polycystic disease in four), compared to two control groups: matched controls and a cohort of recipients with similar kidney disease. During a follow-up period of 60.1 (11.0–76.6) months (median, interquartile range), estimated 5-year survival was 80.8 vs. 96.8%, with and without IBD, respectively ($P = 0.001$). Risk of death with a functioning graft was higher with IBD (HR = 1.441, $P = 0.048$), and with increased age (HR = 1.109, $P = 0.05$). Late rehospitalization rate was higher in IBD [incidence rate ratio = 1.168, $P = 0.030$], as well as rate of hospitalization related to infection [1.42, $P = 0.037$]. All patients that were in remission before KT, remission was maintained. Patients that were transplanted with mild or moderate disease remained stable or improved with Infliximab or Adalimumab treatment. In conclusion, IBD is associated with an increased risk of mortality, hospitalization because of infection and late rehospitalization after KT. Clinical course of IBD is stable after KT.

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Introduction

Inflammatory bowel disease (IBD) is comprised of two major disorders: ulcerative colitis (UC) and Crohn disease (CD). Both disorders have distinct pathologic and clinical characteristics but their pathogenesis remains poorly understood.

The prevalence of inflammatory bowel disease (IBD) in western countries varies between 37.5 to 229/100 000 for UC and 26 to 198.5 cases/100 000 for CD [1,2]. Both diseases are more common in individuals with Jewish ancestry [3,4]. In Israel, the incidence of IBD is greater among European and American-born Jews than among those born in Israel, Asia, or Africa [5–7].

The clinical course of IBD is typically characterized by alternating episodes of flare-up and remission. The prevalence of extraintestinal manifestations in IBD varies from 6% to 46% [8], and can involve almost every

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organ system. Renal involvement has been considered as an extraintestinal manifestation and has been described both in CD and in UC, manifested primarily as urinary calculi and kidney tubular damage [9,10]. Parenchymal kidney disease is not common, but has been well documented in the worldwide literature describing IgA nephropathy as the most common diagnosis [11,12]. Renal insufficiency (defined as serum creatinine >1.5 mg/dl) is a rare but relevant complication in IBD [13]. Kidney transplantation (KT) is considered the treatment of choice for many people with severe chronic kidney disease [14]. IBD *de novo* or as an exacerbation of pre-existing disease is a rare complication after kidney transplantation [15,16]. A multicenter study of IBD and kidney transplantation found no correlation between pre-existing autoimmune disease or immunosuppressive treatment and IBD before or after transplantation [17].

Most of the data on solid organ transplantation in IBD patients refer to liver transplantation, because of the high prevalence of primary sclerosing cholangitis [18]. Reports on IBD patients undergoing renal transplantation are scarce and involve only a small number of patients; the largest published study, to the best of our knowledge, involves only six kidney recipients. [18,19].

Our aim was to investigate the outcome of renal transplantation in IBD patients, in comparison to two control groups: matched-control kidney recipients, and a cohort of kidney recipients with similar primary kidney disease, and to assess the course of IBD after transplantation, in a relatively large cohort of IBD patients (n = 12).

Materials and methods

Study population

The cohort of IBD patients included 12 adult patients who received kidney transplant between 1998–2018 in the Kidney Transplantation unit, Tel Aviv Sourasky Medical Center, with at least 6 months of follow-up post-transplant. In order to compare the IBD patients to similar recipients without IBD, we included two control groups:

The first one was a matched control group, the matching was on a 1:1 ratio, and based on a set of the following criteria:

Year of kidney transplantation (± 12 months), gender (same), age at KT (± 2 years), time on dialysis before KT (± 12 months), and diabetes mellitus prior to KT (same). When more than one possible matched control was identified, the one with the highest similarity according to the above criteria was chosen.

The second control group included all kidney recipients which were transplanted in our center in the same period of time, with similar primary kidney disease, for each cohort: either IgA nephropathy (biopsy proven) or polycystic kidney disease (PKD) proven by imaging. A summary scheme for this study group is presented in Fig. 1. Demographic, laboratory, imaging, and clinical information were obtained from clinical charts. The retrieval of information and publication of these results were approved by the institutional review board and adhered to the ethical principles for medical research involving human subjects of the Helsinki Declaration.

All recipients underwent a comprehensive evaluation including an interview, physical examination, laboratory tests, and imaging before transplantation, according to local protocols. Post-transplantation, all recipients are being followed in our clinic.

Post-transplant Immunosuppression: The program's routine immunosuppression protocols were not modified in patients with IBD. Induction included intravenous corticosteroid therapy with methylprednisolone, and anti-thymocyte globulin in five of 12 recipients (41.7%) or anti-CD25 antibodies in seven of 12 (68.3%). At 1-year post KT, maintenance immunosuppression consisted of low-dose corticosteroids (prednisone 5 mg daily), mycophenolate mofetil (MMF), and calcineurin inhibitors (Tacrolimus) in 11 recipients (91.7%).

The diagnosis of UC and CD was based on the Montréal classification [20]. IBD activity was evaluated clinically before and after KT and was based on endoscopic findings before and after transplantation. Endoscopic assessment for UC was based on the Mayo endoscopic subscore with (0) for inactive disease, (1) for mild disease with erythema, decreased vascular pattern, mild friability, (2) for moderate disease with marked erythema, absent vascular pattern, friability, erosions, and (3) for severe disease with spontaneous bleeding and ulcerations. For CD, endoscopic activity was defined as "remission" in case of the absence of erosions, ulcers and stenosis and fistulas, respectively and "mild" in case of signs of inflammation with erosions and absence of ulcers, stenosis, and fistulas, respectively, and "severe" in case of ulcerations, stenosis, or fistulas. For clinical assessment of CD, the Crohn's Disease Activity Index (CDAI) [21] was used; a score of <150 points was defined as clinical remission. For clinical assessment of UC, the Mayo activity score was used; a score of <4 points was defined as clinical remission [22]. For

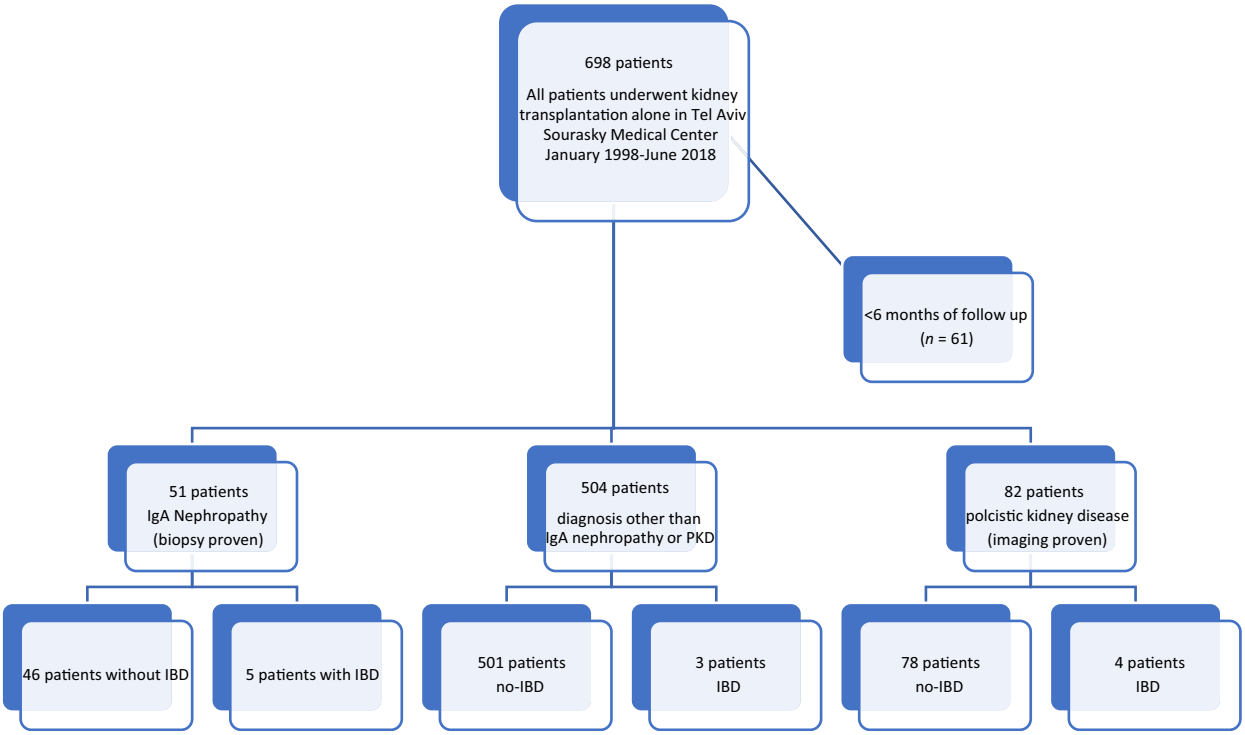

Figure 1 Study scheme.

endoscopic activity, the last endoscopy before KT and the first endoscopy after KT were analyzed.

Early rehospitalization was defined as hospital readmission because of any cause in the first 3 months post-transplant.

Late rehospitalization rate was defined as number of hospital admissions later than 3 months post-transplant, divided by follow-up period (months).

GFR was estimated (eGFR) using the MDRD, and adjusted for body surface area (Mosteller calculation) [23].

Statistical analysis

Continuous variables were expressed as mean and standard deviation or as median and interquartile range (IQR), as indicated. Distribution of continuous variables was assessed using Kolmogorov–Smirnov test and Q–Q plot. Means of two data sets were compared by Student *t*-test if normally distributed and by Wilcoxon if not normally distributed. Proportions were expressed as frequency and percentages and compared by χ^2.

Patient and graft survival in IBD patients were compared with that of patients with similar native kidney disease (polycystic kidney disease or IgA nephropathy respectively) and a group of matched controls, transplanted during the same period of time in our program, and were assessed by means of a Kaplan–Meier plot using the log rank test to assess significance. Logistic regression analysis was used to evaluate associations between nominal outcomes and covariates using the forced entry method. A linear regression model was used to assess correlations to continuous variables. Graft failure was defined as the return of the patient to dialysis and was censored for patient's death. Patient and graft survival were analyzed using the Kaplan–Meier method, and a comparison between IBD and control groups was performed by log rank test. The time of initiation was the renal transplantation date and patients were then followed until last day of follow-up or graft failure or death (the first to occur). Cox regression models were used to evaluate risk factors for patient and graft survival, the variables included in the Cox model were: age at time of transplantation, time on dialysis, and donor type (living versus deceased). Graft failure was defined as the return of the patient to dialysis and was censored for patient's death.

Poisson regression was used to predict late rehospitalizations rate (include patients after the 3rd month post KT), and rate of hospitalization because of infection, weighted by follow-up time, age at KT, and time on dialysis.

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For the matched control group, paired analysis was performed for comparison of baseline characteristics and last day of follow-up (LDFU) parameters.

A two-tailed $P < 0.05$ was considered statistically significant. All analyses were performed with the SPSS 22.0 software (SPSS, Chicago, IL, USA).

Results

All recipients with IBD were Caucasians, a third of them were females, median age at kidney transplantation was 48.4 years and median body mass index (BMI) before KT was 23.7 (IQR 19.4–24.8) kg/cm^2 [23.9 (21.1–25.4) vs. 23.5 (21.4–24.8) kg/cm^2 for DC and UC, respectively, $P = 0.56$]. Two recipients had pre-emptive KT; time on dialysis for all others was 5–48 months. Baseline clinical and laboratory characteristics of the IBD group are shown in Table 1. Five patients were diagnosed with UC and seven as having CD. Out of five patients with UC, four had proctitis in remission without need for chronic treatment or with topical treatment only. One UC patient underwent total procto-colectomy for pancolitis years before and was transplanted with mildly active disease on Infliximab therapy.

Seven patients had Crohn's disease; ileal involvement was documented in all the patients and colonic involvement in four of them. Three patients had documented stricturing and one penetrating disease. Five out of seven patients underwent KT in remission stage. In three, patient remission was achieved on Infliximab therapy and in two on 5-amino-salicylic acid therapy only. Extraintestinal involvement was described in two Crohn's patients and included arthritis and uveitis. These two patients were transplanted during mild and moderately active CD when treated with Infliximab or Adalimumab, respectively.

After KT, 11 of 12 patients received chronic maintenance immunosuppression based on low-dose corticosteroids (5 mg prednisone daily), CNIs (Tacrolimus), and anti-metabolite (mycophenolic acid in nine and mycophenolate mofetil in two). One recipient was on low-dose corticosteroids and Tacrolimus only.

In all nine patients who were in remission before KT, remission was maintained after transplantation without a need for a specific IBD treatment. The clinical activity score for those patients (Mayo activity and CDAI for UC and CD, respectively) remained similar post KT, range 57–93 points for CD, and one point for UC. Patients that were transplanted with mild active IBD (one patient with UC and one with CD) remained stable with Infliximab therapy after KT. The clinical activity score remained two points for the UC patient and decreased from 163 to 110 points to CD patient. One patient who had moderately active CD on Adalimumab before KT improved to mild disease with the same treatment after KT, and CDAI score decreased from 309 to 230 points post KT.

Table 1. Baseline patient characteristics of IBD cohort.

Patient number	Kidney disease	Age at KT	Gender	IBD disease	Intestinal involvement	Extraintestinal involvement	IBD treatment pre-KT	IBD activity pre-KT	Pre-KT activity score*/†
1	PKD	63.4	F	UC	Proctitis	-	5-ASA	Remission	1†
2	IgAN	57.3	M	UC	Proctitis	-	5-ASA	Remission	1†
3	GN	69.4	F	UC	Pancolitis	-	Infliximab, post colectomy	Mild	2†
4	IgAN	36.2	M	UC	Proctitis	-	5-ASA	Remission	1†
5	IgAN	47.1	M	UC	Proctitis	-	-	Remission	1†
6	GN	64.7	M	CD	L3/B2 P	Uveitis, arthritis	Adalimumab	Moderate	309*
7	TMA	41.7	M	CD	L3/B3 P	Uveitis, arthritis	Infliximab	Mild	163*
8	PKD	52.9	M	CD	L1/B2 P	-	Infliximab	Remission	93*
9	PKD	49.6	M	CD	L1/B2 P	-	Infliximab	Remission	84*
10	PKD	43.8	M	CD	L1/B1	-	5-ASA	Remission	98*
11	IgAN	41.6	F	CD	L3/B1	-	5-ASA	Remission	57*
12	IgAN	42.6	F	CD	L3/B1 P	-	Infliximab	Remission	60*

CD, Crohn's disease; GN, glomerulonephritis; IBD, inflammatory bowel disease; IgAN, IgA Nephropathy; KT, kidney transplantation; PKD, polycystic kidney disease; TMA, thrombotic microcytic microangiopathy; UC, ulcerative colitis.

*CDAI (Crohn's Disease Activity Index) used for clinical assessment of CD [18].

†MAYO activity score for assessing ulcerative colitis activity [19].

Primary kidney disease was IgA nephropathy in five patients, PKD in four, glomerulonephritis in two patients, and one presented with thrombotic microangiopathy (Table 1).

Table 2 demonstrates baseline characteristics of the three study groups (IBD group, matched controls group, and cohort of kidney recipient with similar kidney disease: 46 with IgA nephropathy and 78 with PKD, without IBD).

Patients with IBD had a lower BMI compared to both control groups, while other parameters including age, gender, donor type, time on dialysis pre-KT, and induction and chronic immunosuppression were not significantly different.

Clinically significant laboratory data on the last day of follow-up (LDFU), in the study groups, are summarized in Table 3. eGFR, liver function, and platelet counts were comparable between the groups. However, there was a significantly lower mean hemoglobin and serum albumin in the IBD group compared to both control cohorts.

IBD patients were admitted for a longer period of time post-transplantation than non-IBD recipients (median 12 (IQR 8–15) vs. 8 (7–13) days), but the difference was not statistically significant ($P = 0.384$).

Overall, there were nine early rehospitalizations in seven (of 12) IBD patients (58.3%), compared to 55 hospitalizations in 48 controls (38.8%) ($P = 0.224$). The main etiology for early rehospitalization in IBD patients was surgical in 44.4% and infection in 33.3%. In non-IBD, the main etiology for early rehospitalization was surgical in 67.3% and infection in 20%.

Table 2. Baseline characteristics of the study cohorts.

Parameter	IBD, $n = 12$	Matched controls, $n = 12$	*P* value	Similar kidney disease, $n = 124$	*P* value
Age at KT	48.4 (41.9–61.9)	48.9 (40.3–60.9)	0.891	48.8 (38.3–58.9)	0.545
Gender, female (%)	4 (33.33)	4 (33.33)	1	41 (33.0)	1
BMI pre-KT, kg/cm^2	23.5 (21.4–24.8)	25.6 (23.9–28.1)	0.038	25.5 (24.0–28.8)	0.044
Dialysis time pre-KT, months	12 (5–35)	12 (3–42)	0.475	12 (1–37)	0.561
DM pre-KT, (%)	1 (8.33)	1 (8.33)	1	5 (4.0)	0.431
Donor type, living (%)	7 (58.33)	5 (41.66)	0.684	41 (33.0)	0.11
Re-transplant, (%)	2 (16.66)	0 (0)	0.478	13 (10.4)	0.622
Induction, Anti-thymocyte Globulin (%)	4 (33.33)	6 (50)	0.680	21 (16.9)	0.232
Maintenance, (CNIs, Prednisone, MMF), (%)	11 (91.66)	11 (91.66)	1	101 (81.14)	0.692
Median follow-up time (IQR), months	58.3 (21.9–80.8)	62.9 (17.4–85.6)	0.539	66.1 (25.5–135.3)	0.082

Parameters displayed as median (IQR), unless otherwise stated. BMI, body mass index; CNIs, calcineurin inhibitors; DM, diabetes mellitus; IBD, inflammatory bowel disease; KT, kidney transplantation; MMF, mycophenolate mofetil.

Table 3. Laboratory data on the last day of follow-up in the study groups.

Parameter	IBD ($n = 12$)	Matched controls ($n = 12$)	*P* value	Similar kidney disease ($n = 124$)	*P* value
eGFR, ml/min/m^2	53.9 (42.4–65.7)	57.2 (37.9–68.7)	0.361	56.8 (39.6–68.5)	0.557
Serum albumin, g/l	39 (34–41)	42 (39–43)	0.037	42 (39–44)	0.028
Hemoglobin, g/dl	11.9 (9.8–12.0)	13.1 (12.2–15.6)	0.015	13.6 (12.5–15.8)	0.004
Platelet counts, 10e^3/µl	186 (167–226)	191 (172–209)	0.291	189 (143–297)	0.815
Bilirubin, total, mg/dl	0.9 (0.7–1.2)	0.82 (0.7–1.15)	0.311	0.85 (0.73–1.27)	0.714
AST, µ/l	19 (13–39)	16 (10–35)	0.254	17 (10–40)	0.584
ALT, µ/l	17 (11–36)	15 (9–33)	0.373	16 (8–37)	0.439
GGT, µ/l	17 (9–31)	15 (10–32)	0.194	18 (6–33)	0.596

Parameters displayed as median (IQR), unless otherwise stated. ALT, Alanine amino-transferase; AST, Aspartate amino-transferase; eGFR, estimated glomerular filtration rate; GGT, Gamma glutamyl-transferase; IBD, inflammatory bowel disease; PKD, polycystic kidney disease.

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IBD patients had 22 late rehospitalizations in 10 patients, (83.3%), compared to 84 late rehospitalizations in 61/124 (49.1%) in the control group ($P = 0.032$). The leading cause of late rehospitalization was infection in IBD patients (eight urinary tract infection (UTI), four sepsis/bacteremia, two pneumonia, one gastrointestinal tract infection, one CMV, one influenza). One patient was admitted for perianal abscess 4 months post KT (patient number 7, Table 1). In the controls, 51.2% of late hospitalization were because of infection (19 UTI, 13 sepsis/bacteremia, four pneumonia, five gastrointestinal tract infection, one varicella–zoster virus). In a regression analysis, IBD did not significantly increase the risk of early rehospitalization ($P = 0.596$) when assessed following adjustment for age at transplantation and time on dialysis. However, rate of late rehospitalization was significantly higher in IBD [incidence rate ratio = 1.168 (95% CI, 1.004–1.287), $P = 0.030$] and nonsignificantly related to older age [1.28 (0.93–1.89) $P = 0.079$]. IBD also correlated with a higher risk of hospitalization because of infection [1.42 (1.19–1.96) $P = 0.037$] following adjustment for covariates.

Three IBD patients died with a functioning graft during the follow-up period: A 64-year-old female (patient number 1), with UC-PKD, in remission, underwent living unrelated donor (LURD)-KT, and died because of noninfectious encephalitis 14 months post KT.

A 70-year-old female (patient number 3) with UC-glomerulonephritis, in remission after total proctocolectomy with pouch formation and Infliximab treatment, underwent deceased-donor-KT. She was admitted with lower GI bleeding 9 months post KT without evidence of pouchitis on endoscopy and died unexpectedly because of massive aspiration after the procedure.

The third patient, a 67-year-old man (patient number 8) with CD-PKD in remission, underwent a second KT (LURD), and remained in remission on Infliximab post KT. He died 8.5 years post KT because of cardiovascular disease.

Patient survival (adjusted for age at KT and time on dialysis) was inferior in IBD patients compared to both study control groups (Fig. 2). Estimated 5-year patient survival was 80.8 vs. 96.8% for patients with and without IBD, respectively ($P = 0.001$). Risk of death with a functioning graft was higher with IBD (HR = 1.441 [95% confidence interval 1.05–1.631], $P = 0.048$), and with increased age (HR = 1.109 [1.032–1.192] $P = 0.05$).

Death-censored graft survival was comparable between the groups (Fig. 3), and was related to donor type (for living versus deceased donor: HR = 1.27 (1.09–1.836, $P = 0.034$).

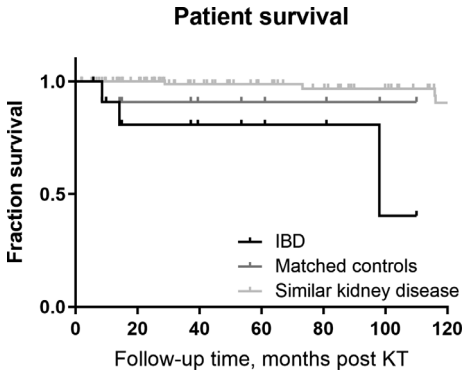

Figure 2 Patient survival for all cohorts, adjusted for age and time on dialysis pre-kidney transplantation. $P = 0.043$.

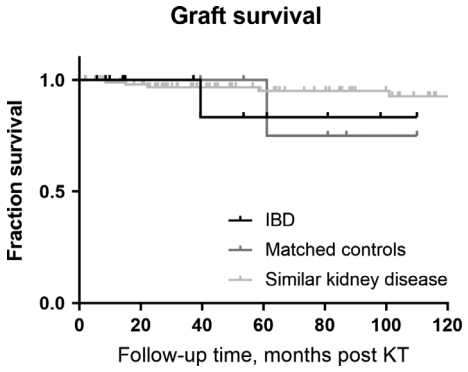

Figure 3 Death-censored graft survival, adjusted for age and time on dialysis pre-kidney transplantation. $P = 0.451$.

Discussion

IBD is a systemic autoimmune disorder, associated with a spectrum of kidney diseases, and patients with IBD have an increased risk of ESRD [24]. Kidney transplantation in an IBD patient is associated with complex medical conditions because of possible influence of IBD on the transplanted kidney, on the patients' survival because of IBD-related complications, or possible need for additional immune suppression to prevent IBD flare ups [25,26]. However, data regarding the outcome of KT in patients with IBD, and IBD course post KT, are scarce and inconclusive, and include small cohorts of patients [18,19]. In this retrospective study, we evaluated kidney transplantation outcome and IBD course post kidney transplantation, in a relatively large cohort of IBD patients who underwent kidney transplantation in our center and were followed up for a median period of 5 years, in comparison with two groups: matched

controls, and non-IBD recipients with similar kidney diseases.

One of the main findings in our cohort was reduced survival and increased rate of late rehospitalizations and hospitalization because of infection in IBD patients post-transplant, compared to controls with similar baseline characteristics including immunosuppression post KT. In an earlier study, Schnitzler *et al.* [18] found in a small cohort of six kidney recipients (five of them CD) an excellent patient survival (no deaths) and graft survival (one graft loss). One possible explanation for the difference in patient survival is an older age at transplantation in our cohort. Indeed, all deaths were in patients older than 65 years old.

In our cohort, the IBD patients had an increased rate of late hospital admissions and infections required admission post-transplant, compared to controls, even after adjustment for age and time on dialysis.

Infectious complications are one of the most common and serious adverse outcomes in IBD patients [27]. In addition to immunosuppression, IBD patients also have a higher risk of infections by virtue of other associated risk factors including malnutrition or need for high-risk interventions such as parenteral nutrition or surgery. Nutritional status, increased age, and other comorbidities are strongly associated with a risk for infection related hospitalizations in IBD patients [27]. Malnutrition is a major complication of IBD [28]. Existing data suggest that malnutrition affects a large portion of patients with IBD, estimated in 65–75% of patients with Crohn's disease and in 18–62% of patients with UC [28–30]. IBD patients, even in remission, have an inferior nutritional status from various etiologies [29–33]. A surgical management in patients with IBD is challenging [34–36], and malnutrition is an important risk factor for postoperative complications and mortality [36–39].

In our cohort, rehospitalizations and hospitalization because of infection were possibly a consequence of a worse nutritional status among IBD patients, as demonstrated by lower BMI, hemoglobin, and serum albumin, or as a consequence of a higher level of chronic immunosuppression status because of the IBD-related treatments.

Although data regarding postoperative complications in IBD patients are related to intestinal surgery, we believe that nutritional status of IBD patients does play an important role in postoperative and late outcome in other types of surgery, like kidney transplantation, and further studies in this field are needed.

We assume that poor nutritional status of IBD patients, as reflected in lower hemoglobin and serum albumin, may be the main reason for the difference in survival in IBD recipients in our cohort and may be indirect evidence of the burden of the disease, even when inactive or mildly active A.

Another possible explanation is that IBD is a chronic systemic illness, related to the glomerular disease (i.e., glomerulonephritis), and as such, after KT the outcome is different to that of isolated kidney disease.

Most of the data regarding IBD course after solid organ transplantation originate from liver transplantation, mainly because of the higher prevalence of primary sclerosing cholangitis in IBD patients [38]. After liver transplantation in these patients, the course is variable and about one-third of patients may experience IBD exacerbation, needing increased medical therapy or even colectomy, while approximately one-third of patients improve [40]. In our cohort, in concordance with Schnitzler *et al.* [18], the IBD course post KT was excellent; most patients remained stable in remission or did not deteriorate. A possible explanation for the excellent course of IBD post KT may be the more intensive immunosuppression, based on MMF, prednisone, and tacrolimus in most patients, compared to less immunosuppression in liver transplantation recipients [18]. Although MMF is well known for its gastrointestinal side effects with characteristic histopathology of IBD-like colitis [41], several studies reported promising results in induction and maintenance of remission in IBD patients [42]. There is a controversy about the efficacy of MMF in active IBD with contradicting results in historical trials [43,44], but it may be considered as a valuable treatment option in IBD patients intolerant of thiopurines [45]. Another hypothesis may be related to the basic activity of IBD: our cohort composed of patients with mild IBD disease, and most recipients were in remission before KT without specific IBD treatments, compared to liver recipients' cohorts composed of patients with more active systemic disease that may be more difficult to control.

Our study has some limitations. First, this is a single center and retrospective study and as such is open to data and selection bias. Second, the sample size, although relatively large, limited the ability for subgroup analysis.

Third, we compared the IBD cohort to two cohorts of kidney recipients: matched controls, who were matched for the main parameters associated with prognosis post KT, and a cohort of recipients with similar kidney disease as most of IBD recipients had, since we

assumed that control based on primary kidney disease will have similar baseline parameters and comorbidities (other than IBD), and different from patients with a systemic disease as the cause of ESRD (e.g., diabetes). Indeed, the main difference between the cohorts was BMI. Those comparison groups may introduce some bias, and together with the relatively low number of participants, the conclusions of the study need to be taken with caution.

In conclusion, in this study, we have found that IBD is associated with increased mortality after kidney transplantation, while death-censored graft survival is comparable to similar kidney diseases. IBD course post kidney transplantation is stable.

Further studies are needed to evaluate these possible connections.

Authorship

AG: conceived the study, reviewed all clinical charts and electronic records, participated in writing of the paper and in data analysis. DS: contributed to study concept and design, interpretation of data, and drafting of the manuscript. RB: contributed to data collection and drafting of the manuscript. IFS: participated in research design, contributed to data collection, and drafting of the manuscript. RN: contributed to data collection and interpretation. YG: contributed to data collection and drafting of the manuscript. PK: contributed to data collection and drafting of the manuscript. AL: contributed to data collection and interpretation. IN: contributed to data collection and interpretation. NL: contributed to data collection and interpretation. JA: contributed to data collection and drafting of the manuscript. MS: contributed to analysis of data and drafting of the manuscript. HK: contributed to study concept and design and acquisition of data, reviewed all clinical charts and electronic records, writing of the paper, and in data analysis. All authors critically reviewed the manuscript and approved it.

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Conflict of interest

All authors declare no conflicts of interest.

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