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Alimentary Tract

Inflammatory bowel disease course in liver transplant versus non-liver transplant patients for primary sclerosing cholangitis: LIVIBD, an IG-IBD study

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ABSTRACT

Background: Data regarding the effect of orthotopic liver transplantation (OLT) for primary sclerosing cholangitis (PSC) on inflammatory bowel disease (IBD) course are scarce and conflicting.
Aims: To compare the incidence of refractory IBD in two groups (OLT and non-OLT) of patients affected by IBD and PSC.
Methods: An observational, multicentre, cohort retrospective study was conducted by the Italian Group for the study of IBD in Italy. The primary outcome was the need for biologic therapy or bowel resection for medically refractory IBD or hospitalization due to IBD relapse during the follow-up. Secondary outcomes were rate of colonic dysplasia, colorectal cancer, other solid tumours, lymphoma.
Results: Eighty-four patients were included in the study. The primary outcome was not different between OLT and non-OLT groups (11/27, 40.7%, versus 20/57, 35.1%, respectively, $p = 0.62$). The lymphoma and other tumours (thyroid cancer, kidney cancer, ileal tumour, ovarian cancer, cervical cancer) rates were significantly higher in the OLT group ($p = 0.04$ and $p = 0.005$, respectively), at the limit of statistical significance for high-grade colonic dysplasia ($p = 0.06$).
Conclusion: OLT in patients affected by IBD and PSC is not a risk factor for a more severe IBD course, but it is associated with a higher occurrence of cancer.

Introduction

Primary sclerosing cholangitis (PSC) is a cholestatic liver disease, which is characterized by chronic inflammation, strictures in intra-, and more often, extra-hepatic ducts and a frequent association with inflammatory bowel disease (IBD), particularly those localized to the colon [1]. In almost 50% of PSC patients, the diag-

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nosis of IBD precedes that of PSC and, after 10 years of follow-up, IBD can be diagnosed in 80% of PSC patients [1], while 3–6% of all IBD patients eventually develop this condition.

There is no medical treatment capable of preventing or modifying the natural history of PSC towards liver cirrhosis and failure: patients with advanced liver disease frequently undergo orthotopic liver transplantation (OLT) [2]. Importantly, around 46% of all patients presenting PSC eventually undergo OLT (2% of overall IBD cases), and 20–50% require a re-transplant (re-OLT) due to PSC recurrence or vascular complications [3].

The management of IBD before and after OLT for PSC can be challenging due to lack of specific guidelines. Experience is based mainly on small studies, but the natural history of IBD after OLT is still poorly investigated, and there are still limited data about the outcome of IBD after OLT [4–7].

The aim of the present study was to compare the incidence of refractory IBD (need for biologic therapy, or surgical resection for medically refractory IBD, or hospitalization) in patients with stable liver disease, not needing OLT, and those with severe liver disease that required OLT. We also investigated possible risk factors for negative outcomes in the IBD-OLT population and the incidence of cancer.

Material and methods

LIVIBD was an observational, multicentre, cohort, retrospective, spontaneous study conducted by the Italian Group for the study of IBD (IG-IBD) in 5 referral centres across Italy.

Patients were eligible if they have had an established diagnosis of PSC and IBD (diagnosed before OLT). PSC was diagnosed according to accepted criteria, with typical findings of bile duct irregularities on cholangiography [8]. The diagnosis of IBD was based on standard clinical, endoscopic, and histopathologic criteria [9,10]. Exclusion criteria were: absence of clinical follow-up documentation, patients diagnosed for IBD after OLT, patients without colonoscopic and histologic sampling supporting an IBD diagnosis, patients without instrumental findings highly suggestive for PSC, OLT due to a disease different from PSC, patients with colectomy for IBD before the start of the follow-up; patients with prior use of any biological therapy; prior intestinal resections before OLT or PSC diagnosis. The primary outcome (i.e. need for biologic therapy, bowel resection, or hospitalization for IBD flare) was compared between OLT and non-OLT groups of patients.

The follow-up period started from 1 year after first OLT in the OLT group (we considered 1 year a reasonable time frame to recover from OLT). In the non-OLT group, the follow-up period started 1 year after the diagnosis of IBD and PSC coexistence. The follow-up was censored at the time of need for biologic therapy (such as anti-tumour necrosis factor [anti-TNF] agents or vedolizumab or ustekinumab), date of bowel resection for medically refractory IBD [11], date of hospitalization for IBD relapse, date of the last follow-up visit or death [12].

We evaluated the following risk factors for refractory IBD in OLT group: sex, duration of illness, smoking habits, type of IBD, number of re-OLT, anti-neutrophil cytoplasmic antibodies (ANCA), IBD localization, disease activity before OLT, different immunosuppressive drugs used after liver transplantation.

Secondary outcomes were rate of colonic dysplasia, colorectal cancer, other solid tumours, and lymphoma.

Statistics

Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were summarized as frequency and percentage. The Chi-square, or Fisher's exact test when appropriate, and the independent samples *t*-test were applied for categorical and continuous variables, respectively.

Table 1
Baseline characteristics ($n = 84$ patients).

	OLT group	Non-OLT group	*p* value
Total patients	27	57	
Age at follow-up, years (mean ±SD)	44.6 ±13.3	44.37 ±16.6	0.96
Male/female, *n* (%)	20 (74.1)/7 (25.9)	39 (68.4)/18 (31.6)	0.60
UC/CD/IBDU, *n* (%)	19 (70.4)/6 (22.2) / 2 (7.4)	31 (54.4)/19 (33.3)/7 (12.3)	0.42
Active smoking, yes (%)	3 (12.5)	10 (17.5)	0.57
Mean FU time, months (SD)	71.9 (74.8)	92.0 (58.3)	0.22
IBD duration, months (mean (SD))	136.0 (116.0)	92.2 (107.4)	0.09
PSC duration, months (mean (SD))	149.5 (76.4)	39.6 (77.9)	<0.001
CD extension, patients *n* (%):	0 (0.0)	5 (26.3)	
L1	1 (16.7)	4 (21.1)	
L2	5 (83.3)	8 (42.1)	
L3	0 (0.0)	2 (10.5)	
L4			
UC extension, patients *n* (%):			
E1	0 (0.0)	2 (6.5)	
E2	3 (15.8)	2 (6.5)	
E3	16 (84.2)	27 (87.1)	
Prior or baseline use of immunomodulators *n* (%)	2 (7.4)	5 (8.8)	

OLT, orthotopic liver transplantation; SD, standard deviation; UC, ulcerative colitis; CD, Crohn's disease; IBDU, inflammatory bowel disease unclassified; FU, follow-up; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis; L1, ileum; L2, colon; L3, ileum + colon; L4, upper digestive tract; E1, rectum; E2, distal to splenic flexure; E3, proximal to splenic flexure.

The comparison between the two groups was performed using the Kaplan–Meier survival curve analysis, so that a minimum follow-up was not required. The follow-up ended at the time of biologics use or colectomy for medically refractory IBD or hospitalization due to IBD flare or at the last follow-up visit. The influence of risk factors on the outcome was analysed with Cox proportional-hazards regression multivariate analysis. As, to our knowledge, there are no studies correlating the clinical course of both Crohn's disease and UC with the necessity of OLT for PSC, or considering the need for hospitalization for IBD recurrence as outcome, a priory calculation of sample size was not possible.

$P < 0.05$ was considered statistically significant. The statistical analysis was performed by using SPSS version 25.

Ethical considerations

The study protocol was approved by the IG-IBD scientific committee, and subsequently, by the Ethical Committee of the coordinating centre (Turin, Protocol N° 0000073; January, 2th 2019), and of each participating centre. All patients received written information and signed the consent for clinical data collection as well as the privacy statement form. Shared database was used for anonymous data collection. The study followed the principles of the Declaration of Helsinki.

Results

Eighty-four patients were eligible for the study and were included in the final analysis. Patient characteristics are shown in Table 1.

The mean age at OLT was 35.1 years (standard deviation, SD = 11.4), rate of re-OLT was 18.5% (5 out of 27 patients, of which 4 patients with 1 re-OLT and 1 patient with 3 re-OLTs; causes of re-OLTs were PSC recurrence, bile duct stenosis, hepatic artery

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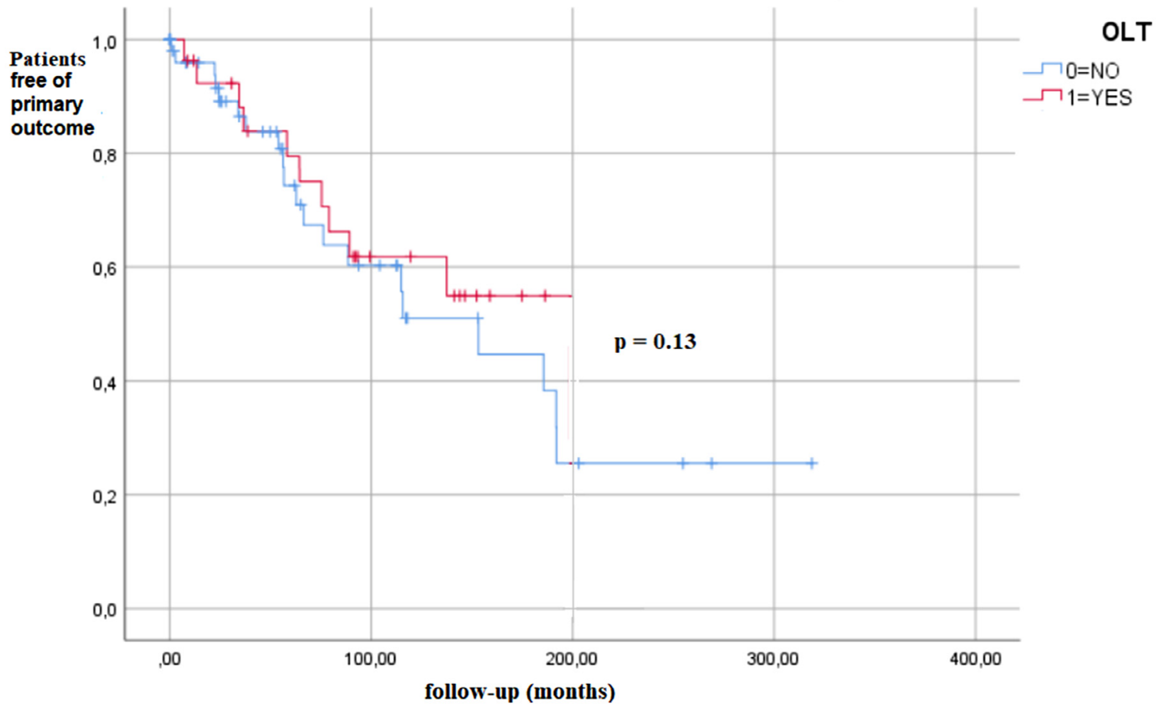

Fig. 1. Comparison between Kaplan–Meier curves (patients free of primary outcome, i.e. need for biologic therapy, bowel resection, or hospitalization for IBD flare) in OLT and non-OLT groups.

thrombosis), mean duration of IBD at OLT was 9 years (range 0–32 years) and mean duration of PSC at OLT was 10 years (range 1–21 years). Regarding anti-rejection drugs, tacrolimus was taken by 21/27 patients (77.8%), mycophenolate by 18/27 (66.7%), cyclosporine by 5/27 (18.5%), everolimus by 5/27 (18.5%), sirolimus by 3/27 (11.1%) and azathioprine by 2/27 (7.4%).

During the follow-up period, IBD relapses requiring biologic therapy were not statistically significantly different in the OLT group compared to the non-OLT group (2/27, 7.4%, versus 11/57, 19.3%, $p = 0.16$). The number of patients requiring hospital admission due to IBD flare was 9/27 (33.3%) in the OLT group, versus 13/57 (22.8%) in the non-OLT group ($p = 0.31$). The rate of colectomy was not different between the OLT and non-OLT groups (4/27, 14.8%, versus 4/57, 7.0%, respectively, $p = 0.27$).

The primary outcome (i.e. the need for biologic therapy, bowel resection, or hospitalization for IBD flare) was not different between the OLT and non-OLT groups (11/27, 40.7%, versus 20/57, 35.1%, respectively, $p = 0.62$; Chi-squared test). Kaplan–Meier curves of OLT versus non-OLT groups confirmed that the primary outcome was not different between the two groups and are reported in Fig. 1.

The risk factors for refractory IBD in the OLT group are reported in Table 2 (not all data were available for the whole cohort; in particular, ANCA result was available in 13 out of 27 patients, smoking habits in 24 out of 27 patients, and IBD activity before OLT in 22 out of 27 patients).

Only non-active smoking status was found to be inversely associated to the risk of refractory IBD in the OLT group ($p = 0.02$). The OLT group had higher prevalence of high-grade colonic dysplasia compared to the non-OLT group (4/27, 14.8%, versus 2/57, 3.5%), although this difference was not statistically significant ($p = 0.06$). In the OLT group, 2/27 patients (7.4%) developed colorectal cancer compared to 1/57 (1.8%) in the non-OLT group ($p = 0.19$). No cases of hepatocellular carcinoma or cholangiocarcinoma were found. Conversely, the rate of lymphoma and of other tumours (thyroid cancer, kidney cancer, ileal tumour, ovarian cancer, cervical cancer) were significantly higher in the OLT group ($p = 0.04$ and $p = 0.005$, respectively). The prevalence of dysplasia and cancer in the two groups is shown in Table 3.

Table 2
Predictors of refractory IBD in OLT group (n = 27).

Predictors	Primary outcome no	Primary outcome yes	*p* value
Sex (F/M)	2/14	5/6	0.06
Non-smokers/smokers/NA	15/0/1	6/3/2	0.02
ANCA (pos/neg/NA)	3/6/7	1/3/7	0.76
UC/CD/IBDU	12/1/3	7/1/3	0.27
IBD duration (mean, SD months)	156.6 (136.7)	106.1 (72.8)	0.28
E2/E3	3/9	0/7	0.14
re-OLT (n/tot)	2/16 (12.5%)	3/11 (27.3)	0.33
Mycophenolate yes (n/tot)	12/16 (75%)	6/11 (54.5)	0.27
Active IBD at OLT (yes/no/NA)	2/11/3	4/5/2	0.13

IBD, inflammatory bowel disease; OLT, orthotopic liver transplantation; F, female; M, male; NA = not available; pos, positive; neg, negative; UC, ulcerative colitis; CD, Crohn's disease; IBDU = IBD unclassified; SD, standard deviation; tot, total; E2, left side colitis; E3, extensive colitis

Table 3
Prevalence of dysplasia and cancer throughout follow-up.

Cancer	OLT group (*n* = 27)	Non-OLT group (*n* = 57)	*p* value
Colonic dysplasia	0 (0)	1 (1.8)	0.40
Low grade (*n*, %)			
High grade (*n*, %)	4 (14.8)	2 (3.5)	0.06
Cancer	2 (7.4)	1 (1.8)	
Colorectal cancer (*n*, %)			0.19
Cholangiocarcinoma (*n*, %)	0 (0)	0 (0)	1
Hepatocellular Carcinoma (*n*, %)	0 (0)	0 (0)	1
Lymphoma (*n*, %)	2 (7.4)	0 (0)	0.04
Other tumours (*n*, %)	5 (18.5)	1 (1.8)	0.005

OLT, orthotopic liver transplantation.

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Table 4
Predictors of more severe IBD course in OLT group at Cox multivariate analysis.

Predictors	H.R.	95% CI	*p* value
Female sex	9.91	0.68–116.17	0.10
No active smoking	0.02	0.00–2.26	0.11
Crohn's disease	9.83	0.31–307.67	0.19
IBD duration	1.00	0.99–1.03	0.53
IBD localization	N.F.		
No re-OLT	0.11	0.005–2.16	0.14
Use of mycophenolate	1.08	0.09–12.64	0.95
No active IBD at OLT	0.84	0.02–32.52	0.93

IBD, inflammatory bowel disease; OLT, orthotopic liver transplantation; H.R., hazard ratio; 95% CI = confidence interval; N.F., not feasible.

Multivariate analysis

Cox multivariate analysis in the OLT group was performed to search for predictors of refractory IBD after OLT. Sex, smoking habits, type of IBD, duration of IBD, disease location, re-OLT, type of immunosuppressant, IBD activity before OLT were considered: none reached statistical significance ($p >= 0.1$) (see Table 4).

Discussion

The impact of OLT on IBD course is controversial. Studies available are quite heterogeneous in terms of study methods, study populations, concomitant immunosuppressive regimens, and follow-up periods. All these limitations do not allow to draw clear conclusions.

Most of the published studies compared UC course in patients before and after OLT without any control group [4,6,13–19] or the outcome was the need for colectomy regardless of intractable UC or cancer [20]. Several studies have shown that UC in patients with PSC tends to be more active in the first 1–3 years after the diagnosis [21]. Therefore, a relatively new diagnosis of IBD seems to be a risk factor for a flare. The first study that analysed the correlation between PSC and UC in 29 patients undergoing OLT was published in 1992 [22]. Most of the patients who had pre-operative active colonic disease continued to suffer from similar symptoms, despite treatment with steroids, cyclosporine, and azathioprine.

An ideal study should include a control group of patients with UC and PSC, without OLT [14]. The only study that compared patients that underwent OLT versus patients who did not require OLT was performed in 96 UC patients [12]. The authors showed that the patients with PSC and UC with severe liver involvement requiring OLT, compared to non-OLT, had a significantly milder clinical course of UC and required fewer drugs (other than mesalazine), and less surgery to control UC activity throughout follow-up. The OLT group also had significantly reduced UC relapses ($p = 0.04$), required fewer courses of steroids for a shorter period, and less patients required azathioprine, compared to the non-OLT group.

We compared patients with IBD undergoing OLT for PSC to a control group of non-OLT IBD patients from a relatively large population. The results of our study confirm the safety of OLT in patients with IBD affected by PSC. We found that the impact of OLT on the disease course is not significant in terms of need for biologics, hospitalization, and colectomy. We also showed that OLT does not increase the risk of severe flares in IBD.

We searched for predictors of refractory IBD after OLT (sex, smoking habits, type of IBD, duration of IBD, disease location, re-OLT, type of immunosuppressant, IBD activity at the moment of OLT), but no predictive factor was identified at multivariate analysis, probably due, in part, to the limited sample size. The impact of heavy immunosuppression required in the OLT population may increase the risk of long-term side effects, such as serious infections and the risk of cancer [23]. We found no significantly increased risk of colonic cancer, but we found a borderline increased risk of colonic dysplasia and a significantly increased risk of lymphoma as well as solid tumours in the OLT population. Thus, adequate surveillance and prevention of solid tumours in this setting of patients are crucial. Clinicians should be aware of this increased risk and discuss with the patient with IBD and OLT about the need for regular monitoring (including close endoscopic follow-up), also considering age, gender, and additional specific risk factors for malignancies.

The ECCO guidelines [23] suggest regular surveillance for patients undergoing immunosuppression and recommend more frequent surveillance for colorectal cancer in patients with IBD and concomitant PSC [24]. PSC is considered an additional risk factor for colonic cancer in patients affected by IBD. However, no data are available on patients undergoing OLT for PSC and concomitant IBD to this regard. Thus, these patients should be closely monitored for this type of complication, probably even more than other patients with IBD [24].

This study has some limitations. Possible selection bias in the observational and retrospective design may result in missing data concerning additional risk factors for the study outcomes. However, all patients eligible for the study were carefully screened in each participating centre. Secondly, the sample size is relatively small, but this reflects the rarity of OLT and PSC in IBD patients. On the other hand, this is the first study directly comparing patients with IBD and OLT with a control group supporting our conclusions. Moreover, our cohort represents real-life patients affected by IBD and PSC usually monitored in referral IBD centres, increasing the validity of our findings.

We can conclude that OLT is not a risk factor for a more severe IBD course in patients with IBD and concomitant PSC, but it may be associated with a higher rate of lymphoma and solid tumours. Specific screening and prevention programs should be considered and investigated in this fragile population. Studies with a larger population and more data are required to further confirm the results of the present study.

Conflict of interest

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