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The impact of ileal-pouch anal anastomosis on graft survival following liver transplantation for primary sclerosing cholangitis

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ABBREVIATIONS:

CI: Confidence interval

DBD: Donation after brain death

DCD: Donation after circulatory death

HR: Hazard ratio

IBD: Inflammatory bowel disease

IPAA: Ileal pouch anal anastomosis

IQR: Interquartile range

IR: Incidence rate

IRA: Ileorectal anastomosis

IRI: Ischaemia reperfusion injury

MELD: Model for end stage liver disease

PSC: Primary sclerosing cholangitis

UC: Ulcerative colitis

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ABSTRACT

Background: Liver transplantation is the only life-extending intervention for primary sclerosing cholangitis (PSC). Given the co-existence with colitis, patients may also require colectomy; a factor potentially conferring improved post-transplant outcomes.

Aim: Determine the impact of restorative surgery via ileal pouch anal anastomosis (IPAA) vs. retaining an end ileostomy on liver-related outcomes post-transplantation.

Methods: Graft survival was evaluated across a prospectively accrued transplant database, stratified according to colectomy status and type.

Results: Between 1990 and 2016, 240 individuals with PSC/colitis underwent transplantation (cumulative 1,870-patient-years until 1st graft loss or last follow-up date), of whom 75 also required colectomy. A heightened incidence of graft loss was observed for the IPAA group vs. those retaining an end ileostomy (2.8 vs. 0.4 per-100-patient-years, log-rank P=0.005), whereas rates between IPAA vs. no colectomy groups were not significantly different (2.8 vs. 1.7, P=0.1). Additionally, the ileostomy group experienced significantly lower graft loss rates vs. patients retaining an intact colon (P=0.044). The risks conferred by IPAA persisted when taking into account timings of colectomy as relates to liver transplantation via time-dependent Cox-regression analysis. Hepatic artery thrombosis and biliary strictures were the principal aetiologies of graft loss overall. Incidence rates for both were not significantly different between IPAA and no colectomy groups (P=0.092 and P=0.358); however, end ileostomy appeared protective (P=0.007 and 0.031, respectively).

Conclusion: In PSC liver transplantation, colectomy+IPAA is associated with a similar incidence rate of hepatic artery thrombosis, recurrent biliary strictures and re-

transplantation compared to no colectomy; whereas colectomy+end ileostomy confers

more favourable graft outcomes.

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic, progressive cholangiopathy for which therapy other than liver transplantation is ineffective (1). Whilst PSC is considered to be a rare disease (2), it is one associated with significant and disproportionate unmet need, wherein ~50% of patients reach a clinical endpoint of death or liver transplantation (3,4). Indeed, PSC accounts for >10% of all United Kingdom liver transplant activity, whilst also being the lead indication for transplantation in Nordic countries (5,6). Although transplantation is a proven life-extending intervention, the incidence of graft loss is significantly greater compared to that observed for non-PSC aetiologies (7).

The vast majority of patients with PSC also develop inflammatory bowel disease (IBD) at some point; predominantly colitis phenotypically (3,8). Whilst the clinical course of gut and liver disease do not necessarily parallel, a series of epidemiological findings indicate that coexistence of colitis is associated with poorer transplant-free survival when compared to PSC patients without an inflammatory bowel disease history (3,9). Moreover, data from a nationwide observational cohort study in Sweden suggests that rates of progression to liver transplantation or death may be lower for patients treated with colectomy prior to PSC-diagnosis (10).

Following liver transplantation, colectomy does not appear protective against graft *per se* (11), although data from several centres indicate that retention of an intact colon, particularly one associated with ongoing inflammatory activity post-transplant,

increases the risk of developing post-transplant complications including disease recurrence and hepatic artery thrombosis (7,12–16).

The definitive, first-line surgical treatment for patients with ulcerative colitis (UC) refractory to medical therapy is a subtotal colectomy (17). This can either be performed leaving an end ileostomy *in situ*; or followed by ileorectal anastomosis (IRA), or restorative proctocolectomy and ileal-pouch anal anastomosis (IPAA). In patients with UC alone, health-related global quality of life is similar for 'well-informed' individuals choosing to retain an ileostomy versus those with a pelvic pouch (18,19), the latter being opted for in approximately 30% of cases (20). This rate has remained relatively constant over the last decade and outcomes are generally good for patients without PSC.

In a Nationwide study from Sweden, the pouch failure rates following restorative proctocolectomy were not significantly different between patients with UC alone vs. PSC/UC (21); although other investigators have reported consistently poorer nocturnal pouch function and worse quality of life scores in the latter group, in addition to high rates of recurrent pouchitis, pouch mucosal atrophy and dysplastic change (22–24). With respect to the post liver transplant setting, 58% to 62% of patients may develop exacerbating features of acute pouchitis (25–27). IRA may also not be favoured given the increased risk of rectal cancer associated with PSC specifically (28,29).

Whilst the frequency of pouch-related complications is well documented in the PSC literature, the impact of IPAA on graft survival following liver transplantation is ill

defined. To this effect, we determined the post-transplant clinical course in PSC patients with an IPAA; specifically compared to those who elected to retain an end ileostomy following their colonic resection, or individuals with colitis yet no colectomy. Our aim was to improve the post-transplant survival estimates for patients and further understand the recipient risk factors contributing to graft loss.

PATIENTS AND METHODS

Study population

We reviewed a prospectively collected, well-characterised database of all adult patients undergoing liver transplantation at the University Hospitals Birmingham NHS Foundation Trust from 1990 up to January 2016. The hospital transplant database is maintained prospectively, details of which can be found elsewhere (30). The immunosuppression protocol for liver transplant recipients across our study period is provided in **Supplementary Table 1**. In order to ensure robustness, accuracy and completeness of data, the transplant database was cross-referenced with an independently accrued registry of all patients having previously attended or under current follow-up of our dedicated PSC clinic. Our intent-to-study population comprised all patients undergoing liver transplantation with PSC and colitis

Details pertaining to IBD and colectomy status (including type IPAA or ileostomy) were collected retrospectively for individuals having undergone colonic resection prior to transplantation, and prospectively in those requiring bowel surgery at any point in the post-transplant course. All those with an intact colon underwent at least one colonoscopy following liver transplantation. Surveillance colonoscopy continued for patients with known colitis, until the point of colectomy or death, in keeping with recommended intervals during the era of clinical follow-up (31,32).

Clinical endpoints

The 'time-dependent' primary clinical endpoint for our study was the incidence rate of first graft loss (death censored). Given the starting point and prolonged observation

period of our study, aetiologies of graft loss were classified broadly, according to hepatic artery thrombosis, recurrent biliary stricturing disease in the absence of hepatic artery occlusion, graft rejection, and primary graft non-function. Secondary endpoints included the incidence rate of recipient mortality, or graft loss / mortality as a combined outcome measure. Patients were censored at the date of last follow-up if they did not meet the clinical endpoint in question.

Statistical analysis

Data are presented using the median and interquartile range (IQR) for continuous variables. The non-parametric Mann-Whitney U-test was used to determine whether significant differences existed between 2 groups, or the Kruskal-Wallis test with Bonferroni-Dunn post-hoc correction with >2 groups. Differences in nominal data were compared by Fisher's exact test. A P value of <0.05 was deemed statistically significant. Risk stratification as pertains to clinical outcomes' analysis was performed through Kaplan-Meier survivorship estimates, and significant differences between groups assessed by Log-rank / Mantel-Cox testing. The proportion of clinical events are presented as incidence rates (IR) per 100-patient-years (pt.-yrs.) with respective confidence intervals (95% CI). Time zero was set at the point of first liver transplantation. Given that colorectal resection may be performed after liver transplantation in PSC, the impact of colectomy 'type' (IPAA or retaining an end ileostomy) was also determined as a time-dependent covariate via Cox regression analysis (33). All data were analysed using IBM® SPSS® v.23.0 (Armonk, NY: IBM Corp.).

Quality control and ethical approval

Completeness, plausibility and validity of the data were independently verified (by PJT, JR and ES), including personalised objective review of all historical medical charts. Local regulatory board approval was obtained prior to study initiation and database/chart review (CAB-04186-12 and CARMS-02246).

RESULTS

Characteristics of the patient population

Over a 26-year observation period, 240 patients with PSC and colitis underwent liver transplantation and comprised our intended study population (175 patients were men; median age of the overall cohort at time of transplant of 47 years [IQR 37 – 57 years]). Across this cohort, we observed 27 incidents of graft loss and 88 recipient deaths over time; yielding a cumulative follow-up until re-transplantation or mortality of 1,870 patient-years and 2,043 patient-years, respectively (**Figure 1**).

Colectomy does not protect against liver graft loss or recipient mortality.

Overall, 31% of patients with PSC and colitis underwent colectomy (n = 75 / 240), either prior to or following first liver transplantation, and before reaching the primary clinical endpoint. Observing the study cohort in its entirety, the incidence of graft loss or patient mortality was no different between the colectomy vs. no colectomy groups (**Figure 2**), even on restricting analysis to those undergoing colonic resection prior to liver transplantation (**Supplementary Figure 1**).

We observed no significant prognostic impact with regard to graft loss conferred by male sex, recipient age at time of transplant or at time of colectomy, pre-transplant MELD score, era in which transplantation was performed, biliary anastomosis type, split liver donation, or organ donation after circulatory death (P value >0.05 for all tested covariates).

The incidence of graft loss is increased for patients with IPAA

Within the colectomy group, 28% (21/75 patients) subsequently underwent creation of an IPAA, akin to the rate reported for UC patients overall (20). Formation of IPAA was more common when colonic resection took place prior to liver transplantation (n = 14/21 vs. 20/54 patients who retained end an ileostomy, P = 0.024), and when surgery was performed at a younger age (39 vs. 49 years, P = 0.001; **Table 1**). Overall, 76 patients (32%) developed at least one episode of acute rejection, with no significant difference between our 3 study groups (Chi-squared P=0.710).

All 21 patients with an IPAA reported deterioration in symptoms related to pouch function, subjectively, within 12 months of liver transplantation. Fifteen/21 patients displayed endoscopically and histologically confirmed inflammation during this time; and all episodes were acute by definition (34), albeit recurrent at a frequency <3 times per year.

Although colectomy overall was not protective, we observed significant differences in the incidence of graft loss between the IPAA patient group (IR: 2.8 [95% CI: 2.0 – 4.5]; 1-, 5-, and 10-year graft loss rates: 85%, 79% and 70%), those without colectomy (IR: 1.7 [1.5 – 2.1], 91%, 88% and 88%) and the ileostomy group (IR: 0.4 [0.3 – 0.5], 1-, 5-, and 10-year graft loss rates: 100%, 98% and 95%) (overall log-rank P value between the three groups = 0.038; **Figure 3**); findings which persisted in sub-analysis only of patients undergoing colonic resection prior to liver transplantation (**Supplementary Figure 2**).

In a direct pairwise comparison, it became apparent that statistically significant differences were attributable to improved liver graft survival experienced by the end ileostomy group versus patients with an IPAA and compared to the no colectomy group (log rank P value = 0.005 and 0.044, respectively) (**Figure 3**). By contrast, the incidence of graft loss was similar between the IPAA group vs. those without colectomy (p = 0.1).

However, when evaluating the impact of colectomy type as a time-dependent covariate in Cox regression analysis, individuals with an IPAA carried greater risk of graft loss versus both the ileostomy (time adjusted HR: 7.32, 95% CI 1.42 – 37.83, P = 0.017) and no colectomy groups (time adjusted hazard ratio [HR]: 3.15, 95% CI 1.17 – 8.50, P = 0.023).

Between our colectomy groups more specifically, IPAA was more often fashioned when the indication for colonic resection was active colitis (**Table 1**). Nevertheless, the negative impact of IPAA on graft survival was retained in a sub-analysis within the latter cohort specifically (**Figure 4)**.

The incidence of post-transplant complications is attenuated in patients retaining an ileostomy, but not an IPAA

Hepatic artery thrombosis (44%) and recurrent biliary stricturing disease (37%) comprised the principal aetiologies of graft loss in our overall cohort, with lesser contributions from primary graft non-function and acute graft rejection (15% and 4%, respectively).

As such, 25 individual patients developed hepatic artery thrombosis (10%); and independently, 75 patients developed recurrent biliary strictures (31%), contributing to 12 and 10 incidents of 1st graft loss, respectively. The event rate of hepatic artery thrombosis was elevated in the IPAA group by greater than fourfold that of the ileostomy group (IR: 2.8 [95% CI: 2.0 − 4.6] vs, 0.6 [95% CI 0.5 − 0.7] per-100-pt.-yrs., respectively; log-rank P = 0.007); but not significantly different compared with the patient cohort retaining an intact colon (IR: 1.5 [1.3 − 1.8] per-100-pt.-yrs.; P = 0.092). No differences were found in the proportion of donors with hepatic artery anomaly across the three groups, although 6 recipients did require formation of an aortic conduit (IPAA, *n* = 1; no colectomy group, *n* = 5). A list of the anatomical variants and arterial reconstruction types performed is provided in **Supplementary Table 2** and **Supplementary Table 3**.

Our institution and others have previously reported a lower incidence of recurrent biliary stricturing disease post-transplant for patients undergoing colectomy (12–14,16). In the present cohort, we found that this potentially protective effect was confined to patients retaining an end ileostomy (**Figure 5A**), whereas the incidence of recurrent biliary strictures was not significantly different between IPAA and no colectomy groups (**Figure 5B**). Episodes of acute rejection did not significantly impact the development of recurrent biliary disease (HR: 1.605, 95% CI: 0.647 − 1.752, P=0.804), neither posed a risk factor for graft loss overall (HR: 0.913, 95% CI: 0.409 − 2.036, P=0.823).

No significant differences were seen across our three groups in terms of patient mortality, or graft loss/mortality as a combined endpoint (**Figure 6**).

DISCUSSION

In Europe and North America the burden of PSC on liver transplant services is substantial, given a critical absence of effective medical therapy. A societal impact is also evident given the high frequency with which graft loss occurs relative to other aetiologies (15,35). As clinicians we strive to provide the best donor organ possible to our patients, as well as identify putative risk factors for loss that sit with the recipient. An interesting observation is the fact that persistence of colitis after transplantation may increase the risk of biliary disease recurrence (12–14,16), although this does not always translate to changes in graft survival. Indeed, many individuals still experience graft loss in the absence of recurrent PSC and despite undergoing colectomy (11).

To further understand the clinical course that patients experience, and to offer better counselling specifically to those needing colonic resection, we examined the impact of colectomy type across a large PSC/UC transplant cohort. In so doing, we identify IPAA as a significant risk factor for graft loss, even for patients undergoing colectomy prior to transplantation or when the impact of colectomy type was determined in time-dependent covariate analysis. Conversely, graft survival was maximised in the colectomy group retaining an end ileostomy.

The main aetiologies necessitating re-transplantation in our studied cohort were hepatic artery thrombosis or recurrent biliary disease. As discussed, the presence of an intact colon has been put forward as a risk factor for the latter (12–14,16), albeit inconsistently validated (11,36,37). Herein, we identify that any protective effect conferred following colectomy (with regard to recurrent biliary disease) is skewed

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toward the patient group retaining an end ileostomy, whereas no benefit is evident for patients with an IPAA. As patients with PSC and IPAA often develop pouchitis and poorer pouch function (23), it is plausible that persistent or recurrent episodes of intestinal inflammation also contribute to an elevated risk of thrombotic injury, akin to that when the colon is retained (7,12–14,16,38). Although speculative, evidence to support this hypothesis includes the fact that our ileostomy group experienced the lowest incidence of hepatic artery thrombosis; in addition to findings that show persistent subclinical intestinal inflammation in PSC associated colitis (39,40), associations between pouchitis and thrombocytosis (41), and heightened platelet activation during active IBD (42).

Whilst speculative, our data argues against the fact that an aggressive 'liver phenotype' post-transplant is driven purely by predisposition toward aggressive IBD. This is because colectomy overall, a marker of colitis activity in its own right, was in itself not a risk factor for re-transplantation. Instead, the negative impact on graft outcome was associated with either (a) retaining an intact colon post-transplant, and by proxy, persistence of ulcerative colitis as a comorbidity; or (b) formation of IPAA in the event colectomy was performed. Detailing the pathogenic mechanisms of PSC and pouchitis are beyond the scope of the current study, but of interest, mucosal dysbiosis has been called into question in both conditions (43). Whether unique commensal disturbances correlate with risk of allograft recurrence, thromboembolic events or actual graft loss, is also an area of ongoing investigation (44). Given the increased incidence of hepatic artery thrombosis in patients with PSC and IBD (7,38), which we now confirm is relevant to those with IPAA, a dedicated evaluation of thrombotic tendency is needed in this at-risk population (45).

An early study from the Mayo clinic indicated a 10-year graft loss rate of 12.5% for transplanted PSC patients with an IPAA (46). The Cleveland Clinic have also published their experience; and in a total cohort of 79 transplanted PSC patients they also found an increased frequency of hepatic artery thrombosis (27% in the IPAA group vs. 18% in the no colectomy group) although surprisingly none went onto be re-transplanted, and a comparative outcomes' analysis against a control ileostomy group was not presented (27). By contrast, ours is also the first study to robustly determine the impact of colectomy status and type in a time-dependent outcomes' analysis for patients with PSC/UC and show improved graft survival when patients elect to retain an ileostomy.

In selected studies, acute rejection has also been linked to development of recurrent biliary disease post-transplantation (15), and it is conceivable that alloreactive immune responses may recruit long-lived memory T-cells from the gut implicated with the development of PSC prior to transplantation. Alternatively, abrupt changes in immunosuppression while treating rejection may trigger immune reconstitution and subsequent reactivity to biliary epithelial antigenic epitopes associated with the development of recurrent disease. However, links between acute rejection and recurrent disease are inconsistently validated; and despite poorer outcomes in our IPAA group, acute rejection occurred at a similar frequency to those having an ileostomy or without colectomy. Moreover, no causal relationship was identified between acute rejection and development of either recurrent biliary disease or graft loss overall.

The therapeutic arena of IBD continues to evolve, and with regards to PSC/colitis specifically, a wealth of attention has focussed in targeting the integrin α4β7 (47,48). Although this strategy may not impact liver biochemistry (47), the potential role in attenuating disease progression is of particular interest given that recruitment of α4β7$^+$ mucosal lymphocytes are implicated in the pathogenesis of PSC liver disease (49), including recurrence post-transplantation for patients with colitis and an intact colon (15).

Whilst a single centre report, the Birmingham liver unit contributes 25% of all liver transplant activity in the United Kingdom (5). Our transplant database is maintained prospectively but we nevertheless lack historical data such as quantifiable IBD severity scores, extent of colonic involvement and pharmacological treatment regimens; neither have we accrued details on IPAA function and quality of life indices, or severity of liver disease at the time colectomy was undertaken. This is because the tertiary referral nature of our transplant unit means that for many patients, IBD care delivery was undertaken at a different centre. An additional restriction is the fact that our IPAA group contains a limited number of patients, precluding multivariable analysis of robust statistical power. Unlike reports from other centres (21), our cohort was also devoid of an IRA group. This is because in PSC/UC, IRA is associated with a >6-fold risk of developing rectal cancer compared to IRA in UC alone (28); leading to avoidance in fear of malignant degeneration. A further limitation is that our prospectively captured data records did not include incidence or severity of ischaemia-reperfusion injury (IRI) specifically, a factor which may have reduced graft viability for certain individuals. Nevertheless, when IRI leads to early graft loss, this is as a result of primary graft non-function. The latter occurred in a

total of 4 patients across our entire study cohort, all within the no colectomy group (vs. no patient with an IPAA or ileostomy). Moreover, the greatest risk of IRI is in the context of organ donation using marginal grafts, mainly livers donated after circulatory death (DCD); whereas all patients within our IPAA group were recipients of organ donation after brain death.

We must also be mindful that our prolonged study period parallels the evolving indications for liver transplantation. For instance, the Model for End Stage Liver Disease (MELD) score was only developed in the year 2000 (50,51), and not captured for the few within our cohort transplanted prior to January 1994. A similar caution applies to the progressive knowledge that surrounds transplant-related complications. Consequently, we evaluated the incidence of all recurrent/non-anastomotic biliary strictures collectively, for attributing more specific labels to lesions that developed in the early 1990s (for instance, differentiating ischaemic-type biliary lesions from recurrent PSC) may neither be correct nor consistent with contemporary definitions and imaging modalities (7,13). In any event, the lack of 'protocol' cholangiographic/angiographic surveillance is caveat across most outcome studies in transplantation including our own, and it is conceivable that the sub-clinical incidence of vascular events and biliary complications is higher than actually reported.

The decision to undergo pouch formation is largely a surgical consideration led by patient choice (52). However, given an era of organ shortage in liver transplantation, we advocate that all with PSC who require colorectal resection be counselled about potential risks of poorer pouch function compared to UC alone (23), and also the relatively increased incidence of graft loss; although we

cannot be certain of a definite causal relationship between existing pouch and liver transplant failure at this stage. In light of our study findings, the impact of IPAA, pouch function and pouchitis on clinical events as relate to the native liver in PSC also requires investigation, and represents an area of ongoing research activity. Further prospective and independent validation is of the utmost importance in these areas, and ideally should proceed via multi-centre collaborative networks and across a globally representative patient population (3).

CONFLICTS/STATEMENT OF INTEREST:

None

Table 1: Characteristics of PSC / UC patients undergoing liver transplantation"

	IPAA (*n* = 21)	End ileostomy (*n* = 54)	UC but no colectomy (*n* = 165)
Male sex	19 (90%)	44 (81%)	112 (68%)
Recipient age at time of liver transplant, years	41 (34 – 55)	49 (42 – 56)	47 (35 – 59)
MELD score pre-transplantation**	17 (12 – 27)	16 (11 – 21)	13 (10 – 19)
Era of transplant			
- 1990 – 2000	8 (38%)	20 (37%)	50 (30%)
- 2000 – 2010	8 (38%)	21 (39%)	51 (31%)
- 2010 – 2016	5 (24%)	13 (24%)	64 (39%)
Organ donation after circulatory death	0 (0%)	2 (4%)	20 (12%)
Living-related organ donation	0 (0%)	0 (0%)	2 (1%)
Split liver donation	1 (5%)	3 (6%)	18 (11%)
Duct-to-duct biliary anastomosis	3 (14%)	8 (15%)	17 (10%)
Episode of acute rejection	5 (24%)	18 (33%)	53 (32%)
- Greater than 1 episode of acute rejection	1	2	9
Age at time of colectomy, years	39 (IQR 33 – 43)	49 (IQR 39 – 58)	
Era of colectomy			
- 1990 – 2000	11 (52%)	15 (28%)	
- 2000 – 2010	6 (29%	22 (41%)	
- 2010 – 2016	4 (19%)	17 (31%)	
Colectomy post liver transplant	7 (33%)	33 (61%)	
Colectomy indication			
- Active colitis	20 (95%)	35 (65%)	
- Dysplasia / neoplasia	1 (5%)	12 (22%)	
- Combination	0 (0%)	4 (7%)	
- Other	0 (0%)	3 (6%)	

Abbreviations:
IPAA, ileal-pouch anal anastomosis; MELD, model for end-stage liver disease score; UC, ulcerative colitis

*MELD scores not captured for procedures performed prior to January 1994 (n=36/240; n=2, 6 and 28 patients in the IPAA, end ileostomy and no colectomy groups, respectively).

Figure 1: Clinical outcomes following liver transplantation for primary sclerosing cholangitis

Kaplan-Meier estimates illustrating the incidence of [A] graft loss, [B] patient mortality, and [C] graft loss / patient morality as a combined endpoint in our overall PSC/colitis cohort undergoing liver transplantation. Incidence rates are presented per 100-patient-years and the respective 95% confidence intervals. Event-free survival rates are calculated using the life-tables method. Time zero is set from the point of liver transplantation.

Abbreviations: PSC (primary sclerosing cholangitis), Pt. yrs. (patient years), Pts. at risk (patients at risk)

Figure 2: Post liver transplant clinical course according to colectomy status

Kaplan-Meier estimates stratified according to colectomy status for all transplanted PSC patients with colitis; specifically for graft loss only [A], mortality only [B] and graft loss/mortality as a combined clinical endpoint [C]. Incidence rates are presented per 100-patient-years and the respective 95% confidence intervals. Event-free survival rates are calculated using the life-tables method. Time zero is set from the point of liver transplantation.

Abbreviations: PSC (primary sclerosing cholangitis), Pt. yrs. (patient years), Pts. at risk (patients at risk)

Figure 3: Liver graft loss rates following transplantation according to colectomy type.

Kaplan-Meier survival estimates of liver graft loss stratified by colectomy type for all transplanted PSC patients with colitis. Incidence rates are presented per 100-patient-years and the respective 95% confidence intervals. Event-free survival rates are calculated using the life-tables method. Time zero is set from the point of liver transplantation. Results of the overall log rank test are presented in the graphic. Outcome of testing in a pairwise Log rank test are as follows: IPAA vs. the ileostomy group; $P = 0.005$; no colectomy vs. the ileostomy group; P value = 0.044 and IPAA vs. no colectomy group, $P = 0.1$.

Abbreviations: IPAA (ileal pouch anal anastomosis), PSC (primary sclerosing cholangitis), Pt. yrs.   (patient years), Pts. at risk (patients at risk)

Figure 4: **Liver graft loss rates following transplantation in patients undergoing colectomy for medically refractory colitis.**

Kaplan-Meier survival estimates of liver graft loss specifically in PSC patients who underwent colectomy for medically refractory colitis and stratified by colectomy type. Incidence rates are presented per 100-patient-years and the respective 95% confidence intervals. Event-free survival rates are calculated using the life-tables method. Time zero is set from the point of liver transplantation.

Abbreviations: IPAA (ileal-pouch anal anastomosis), PSC (primary sclerosing cholangitis), Pt. yrs. (patient years), Pts. at risk (patients at risk)

Figure 5:   **Incidence of recurrent biliary strictures post-transplant**

The incidence of recurrent biliary strictures that developed in the absence of hepatic artery occlusion is shown for the overall cohort, stratified by colectomy type. Event rates are depicted for the no colectomy vs. ileostomy group in [A], and no colectomy vs. the IPAA group in [B]. Incidence rates presented per 100-patient-years and the respective 95% confidence intervals. Event-free survival rates are calculated using the life-tables method. Time zero is set from the point of liver transplantation.

* 5 / 54 patients in the ileostomy group underwent their colectomy following development of a recurrent biliary stricture, and thus re-assigned to the 'no colectomy' group for this analysis.

Abbreviations: IPAA (ileal-pouch anal anastomosis), PSC (primary sclerosing cholangitis), Pt. yrs. (patient years), Pts. at risk (patients at risk)

Figure 6: **Combined patient and graft survival rates**

Kaplan-Meier survival estimates of patient mortality [A] and patient mortality / graft loss as a combined endpoint [B] stratified by colectomy type for all transplanted PSC patients with colitis. Incidence rates are presented per 100-patient-years and the respective 95% confidence intervals. Event-free survival rates are calculated using the life-tables method. Time zero is set from the point of liver transplantation.

Abbreviations: IPAA (ileal-pouch anal anastomosis), PSC (primary sclerosing cholangitis), Pt. yrs. (patient years), Pts. at risk (patients at risk)

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