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Differences between infectious disease events in first liver transplant versus re-transplantation in the Swiss Transplant Cohort Study

Short title: ID events in liver re-transplantations

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Abstract

Background & Aims: Re-transplantation after graft failure is increasingly performed, but inferior graft survival, patient survival and quality of life has been reported. The role of infectious disease (ID) events in this less favorable outcome is unknown.

Approach & Results: We analyzed ID events after first liver transplantation (FLTpx) and re-transplantation (re-LTpx) in the Swiss Transplant Cohort Study. Clinical factors were compared after FLTpx and re-LTpx, survival analysis was applied to compare the time to ID events after FLTpx and after re-LTpx, adjusted for age, gender, MELD score, donor type, liver transplant type (whole vs. split liver) and duration of transplant surgery.

In total, 60 patients were included (65% male, median age of 56 years). Overall, 343 ID events were observed, 204 (59.5%) after the FLTpx and 139 (40.5%) after re-LTpx. Bacterial infections were most frequent (193/343, 56.3%), followed by viral (43/343, 12.5%) and fungal (28/343, 8.2%) infections, with less infections by *Candida* spp. but more by *Aspergillus* spp. after re-LTpx (P-value = 0.01). The most frequent infection site was bloodstream infection (86, 21.3%), followed by liver and biliary tract (83, 20.5%) and intraabdominal (63, 15.6%) infections, After re-LTpx, more respiratory tract and surgical site infections were observed (P-value < 0.001). The time to first infection was shorter after FLTpx (adjusted hazard ratio (HR) = 0.5 [confidence interval: 0.3, 1.0], p = 0.04). Reduced hazards for ID events after re-LTpx were also observed when modelling recurrent events (adjusted HR = 0.5 [0.3, 0.8], P-value = 0.003).

Conclusions: The number of infections was comparable after FLTpx and re-LTpx, however, differences regarding infection sites and fungal species were observed. Hazards were reduced for infection after re-LTpx.

Introduction

Re-transplantation after graft failure of a previous transplant has become a valuable option. Current data suggest that transplant-related outcomes, such as graft survival or patient survival and quality of life are inferior after re-transplantation, as compared to the first transplantation (1–4). Broschewitz et al (3) compared the health-related quality of life (HRQoL) in patients who received a primary liver transplant and liver re-transplantation and found that the HRQoL was significantly lower in re-transplant patients, suggesting that not all patients benefit from re-transplantation. Similarly, Marudanayagam et al (5) found no survival benefit in second or third transplantation when analyzing data on liver transplantations collected over 25 years.

Despite an increase in re-transplantation (2,4), data on infectious disease (ID) events after the initial transplantation as compared to re-transplant are scarce. Infections are a major threat for both graft and patient survival (6). Several factors may contribute to a higher risk of infections following re-transplantation. These patients have been already exposed to immunosuppressive treatment since the first transplant, which might render them more prone to infections. Furthermore, re-operation is likely more complex, resulting in prolonged duration, which in turn increases the risk of a surgical site infection (7). Due to the paucity of available data, definite conclusions are lacking. Identification of additional risk factors for ID events after re-transplantation might help to optimize post-transplant care, e.g. by implementation of specific preventive measures. Moreover, an improved understanding of infectious complications after re-transplantation might facilitate optimized organ allocation.

Our study aimed to describe all ID events in patients who received liver re-transplantation. We studied differences regarding ID events, e.g., type of pathogen and infection site, after first liver transplantation (FLTpx) and after liver re-transplantation (re-LTpx). Moreover, we compared ID events after FLTpx and after re-LTpx to address the question of whether ID events are more frequent after re-LTpx.

Methods

Swiss Transplant Cohort Study (STCS)

The STCS (www.stcs.ch) is a prospective cohort study collecting data and biosamples of transplant recipients in all six transplant centers in Switzerland (Basel, Bern, Geneva, St. Gallen, Lausanne and Zurich) (8). Liver transplantation takes place in only 3 of 6 transplant centers (Basel, Geneva, and Zurich). The STCS was approved by the Ethics Committees of all participating institutions. For this nested study, a separate approval by the responsible Ethics Committee (Kantonale Ethikkommission Zürich) was obtained

(Req. 2019-00248). Informed consent was signed by all patients prior to transplantation. Liver transplant recipients between May 2008 and December 2019 (STCS download: July 2020) were included in this study. All data used in our study were prospectively collected. In particular, ID events were prospectively recorded by dedicated professionals supervised by transplant infectious diseases physicians using uniform definitions (9).

Study population

All adult (≥18 years of age at the time of their FLTpx) liver transplant recipients who had their FLTpx and re-LTpx recorded in the STCS were included in this study. We excluded patients with liver re-LTpx if information on the FLTpx was missing, e.g., FLTpx prior to May 2008. Patients who experienced a re-LTpx due to a primary nonfunctioning graft were also excluded (See **Figure 1**).

Infectious disease events

A discrete infectious disease event was defined as a clinical presentation attributable to an infection in combination with detection of a causative pathogen (except for probable infections) (9). The repeated detection of an identical pathogen in temporal context, e.g. prolonged bacteremia, was considered as one discrete event. A recurrent infection was reported as an additional ID event if the recurrence occurred after completed sufficient treatment (and termination of secondary prophylaxis for CMV) of the anteceding infection. In particular, the following ID events, as previously defined (9), were included: 1) proven bacterial infections, i.e., clinically apparent infections combined with detection of the causative bacterium and initiation of targeted antimicrobial treatment 2) symptomatic viral infections 3) proven, probable and possible invasive fungal diseases (IFD; according to EORTC/MSG criteria) fungal infections (10) and 4) probable infections, defined as clinical presentations with suspected infectious etiology resulting in initiation of antimicrobial treatment by the treating physicians, if routine diagnostics failed to identify a causative pathogen. For all viral infections, exclusively symptomatic viral infections were included, which required the detection of the viral pathogen, e.g., by polymerase chain reaction or biopsy, and the presence of symptoms attributable to this viral pathogen. For EBV, hepatitis, CNS manifestations, hematological manifestations and PTLD were considered. We excluded infections caused by hepatitis C (HCV) for all patients who underwent transplantation because of HCV infection, as without prior HCV treatment an infection of the graft was expected. Moreover, we excluded ID events that were already present on the day of transplantation.

Statistical analysis

Comparison of characteristics after FLTpx versus re-LTpx: We compared several characteristics, e.g., the distribution of pathogen types and infection sites, after the FLTpx versus re-LTpx. Categorical variables

were compared using the Chi-squared test or McNemar-test (for specific sites). Continuous variables, e.g., MELD (Model for end-stage liver disease)-score after FLTpx and re-LTpx were compared using paired Wilcoxon tests.

Frequency of ID events after FLTpx versus re-LTpx: First, we used a Cox proportional hazards model to determine the time to the first ID event after the FLTpx and re-LTpx. Secondly, we used the Andersen-Gill counting process to model recurrent ID events, with the time period (after FLTpx or after re-LTpx) being an explanatory variable (11). We assumed that ID events are correlated within individuals. Since correlation of ID events might differ between different pathogens, we performed a sensitivity analysis repeating the analysis assuming independence of ID events within individuals. In a multivariable analysis, we adjusted for age, gender, MELD score, donor type, liver transplant type (whole vs. split liver) and duration of transplant surgery. All covariables were included specific to the relevant time interval: in the interval between FLTpx and the re-LTpx, donor type, liver type etc. from the FLTpx were considered, in the second interval after re-LTpx, the variables concerning the re-LTpx were considered. We used the R package survival (12,13) for all Cox models.

Results

Study Population

Among 121 patients with a re-LTpx recorded in the STCS, there were 78 patients with both the FLTpx and a re-LTpx documented in the cohort. Of those, 60 were included and represented the final study population; 18 patients were excluded due to primary nonfunctioning graft (**Figure 1**). The majority of the study population was male (39, 65.0%), of Caucasian ethnicity (56, 93.3%) and the median age at FLTpx was 56 years. The median time between FLTpx and re-LTpx was 0.7 years (range = [0.0, 10.6]) (**Table 1**). Most frequent reasons for FLTpx were HCV (16, 17.6%), hepatocellular carcinoma (7, 7.7%) and hepatitis B (5, 5.5%), and for re-LTpx chronic cholestasis (15, 16.5%) and ischemic hepatopathy (13, 14.3%). Median MELD-score was 15 (range = [6, 40]) at FLTpx and 24.0 (range = [7, 40]) at re-LTpx (P-value: < 0.001). At re-LTpx, more grafts derived from brain dead donors (P-value= 0.001) and fewer split livers were used (P-value: < 0.001. Hepato-renal syndrome was more frequent at re-LTpx (P-value= 0.019). Prophylactic strategies were identical for cytomegalovirus (CMV) using a preemptive approach, with the exception of high-risk constellation (CMV donor positive / recipient negative) prompting a prophylactic approach. Routine primary antifungal prophylaxis was not used in any of the centers. With the exception of a single center, which administered routine trimethoprim/sulfamethoxazole prophylaxis only in individuals with a MELD > 30, after administration of ATG, or after re-LTpx, the other two participating centers prescribed trimethoprim/sulfamethoxazole prophylaxis for 6 months after both, FLTpx and re-LTpx.

Infectious disease events

Of all 60 patients, 19/60 (31.7%) patients did not experience any ID event after FLTpx nor re-LTpx, while 15/60 (25.0%) patients had ID events only after FLTpx and 6/60 (10.0%) only after re-LTpx, and 20/60 (33.3%) after both transplantations. Of the patients who had at least one ID event, the median number of ID events was 6 (range = 1 - 54), with a median of 5 (range = 1 - 22) after FLTpx and 3 (range = 1 - 35) after re-LTpx (**Figure 2**). There were 343 ID events documented: 204 (59.5%) infections were observed after the FLTpx and 139 (40.5%) infections occurred after liver re-LTpx.

Bacterial infections were most frequently observed (193/343, 56.3%), followed by viral (43/343, 12.5%) and fungal (28/343, 8.2%) infections (**Figure 2**). Among bacterial infections, the most frequent organisms were enterococci (72/193, 37.3%), *Escherichia coli* (29/193, 15.0%) and *Klebsiella* spp. (18/193, 9.3%). The most common viral pathogens were CMV (11/43, 25.6%) and herpes simplex virus (HSV) (8/43, 18.6%). There was no significant difference in the distribution of different bacterial pathogens (P-value = 0.13) or viral pathogens (P-value = 0.06) after the FLTpx and re-LTpx, but differences in the distribution of fungal species (P-value = 0.013) (**Table S1**). Following re-LTpx fungal infections caused by *Candida* spp. decreased, whereas *Aspergillus* spp. increased.

The most frequent infection site was bloodstream infection (86, 21.3%), followed by liver and biliary tract (83, 20.5%) and intraabdominal (63, 15.6%) infections (**Table S2**). There was a significant difference in the distribution of infection sites when comparing ID events after FLTpx versus re-LTpx ($p < 0.001$). While intraabdominal infections contributed to 20.7% of all ID events after FLTpx, this was the case in only 8.7% of ID events after re-LTpx (P-value: < 0.001). Respiratory tract infections comprised 17.4% of all ID events after re-LTpx, in comparison to 7.3% of ID events after FLTpx (P-value: < 0.001). Surgical sites infections were more common after re-LTpx (14.0%) as compared to after FLTpx (3.9%; P-value: < 0.001).

Time-to-event analysis: ID events after FLTpx *and after re*-LTpx

The time to the first ID event after re-LTpx (median 25.5 days) was longer as compared to FLTpx (median 24 days, adjusted hazard ratio, HR = 0.5 [0.3, 1.0], P-value = 0.04). The same was observed when restricting to bacterial infections (**Figure 3**). When modelling recurrent ID events, there was a significantly reduced hazard for ID events after re-LTpx (unadjusted HR = 0.5 [0.4, 0.8], P-value = 0.004, adjusted HR = 0.5 [0.3, 0.8], P-value = 0.003) (**Figure 3**).This effect remained significant when restricting to bacterial infections in the univariable analysis (HR = 0.6 [0.4, 0.9], p = 0.03) and weakened after adjustment (adjusted HR = 0.7 [0.4, 1.1], p = 0.09). These findings were robust concerning the removal of outliers (removal of one extreme outlier, and removal of the four patients with 20 or more ID events, see **Appendix**

Section 4.1-4.4). Moreover, the findings were robust regarding the assumption of ID events being correlated or not within individuals (see **Appendix Section 4.5**).

Discussion

In the present cohort study encompassing 60 liver transplant recipients that received a re-LTpx, we observed a comparable number of infections after FLTpx and re-LTpx. Following re-LTpx, a reduced hazard for infections was observed.

After both FLTpx as well as re-LTpx, the vast majority of infections were caused by bacteria, followed by viruses and fungi. Interestingly, fungal infections caused by *Candida* spp were more frequent after FLTpx, whereas aspergillosis was more common after re-LTpx. Similarly, Marti J et al. reported bacterial infections followed by viral infections most frequent after both, FLTpx and re-LTpx, in a retrospective study focussing on liver transplant recipients for HCV (14). In line with our findings, this study did not identify any significant difference in the number of ID events overall nor for the subsets of bacterial and viral infections. The authors only provided aggregated data on fungal infections without a relevant change between FLTpx and re-LTpx. In a retrospective, single centre study from Germany, bacteria also caused the majority of infections among liver re-transplant recipients, followed by fungal infections in the early post-transplant period and viral infections in the late post-transplant period, respectively (15). This distribution of pathogens resembles to the findings across all transplant organs recorded in the STCS, which was recently described by van Delden C et al (9).

Consistent with prior observations, liver and biliary tract, bloodstream, and respiratory tract infections were most frequently observed after re-LTpx (15). Compared to FLTpx, more respiratory tract and surgical site infections were observed after re-LTpx. However, the reasons for the observed significant difference of the distribution of infection sites between FLTpx and re-LTpx are not known. The higher frequency of surgical site infections after re-LTpx might be explained by a more complex intervention with prolonged duration of surgery e.g. due to adhesions resulting in a higher risk of surgical site infection.

Notably, a reduced hazard for all types of infection combined was detected after re-LTpx, as well as restricted to proven bacterial infections. Several studies suggest a correlation between different ID events within individuals (16–18). For example, in a mouse model, latent CMV reactivation was observed after induced abdominal infection; the authors speculated that this reactivation is triggered by cytokines, antigenic stimulation, catecholamine excess and shock (16). Similarly, cytokines were found to be involved in reactivation of latent herpesvirus infections during helminth infections (18). Increasing evidence supports a relevance of CMV infection for the development of invasive fungal diseases (19). Invasive

aspergillosis, *Pneumocystis jirovecii* pneumonia and candidemia are the most frequently reported invasive fungal diseases after solid organ transplantation (19). Already in 1997, George MJ et al reported CMV disease as independent risk factor for invasive fungal diseases among liver transplant recipients (20). Similarly, CMV viremia has been associated with a higher risk of *Pneumocystis jirovecii* pneumonia (21). These studies hence suggest ID events within individuals to be, at least partly, correlated. However, considering the uncertainties regarding the degree of independence or correlation of infections, we performed a sensitivity analysis assuming independence of ID events. Again, we observed a decreased hazard for infections after re-LTpx, indicating that our results are stable irrespective of the degree of correlation between ID events.

The observation that certain individuals experienced a series of infections, whereas other liver transplant recipients had no infection could be due to several reasons. On one hand, this finding might reflect a certain degree of correlation between ID events. On the other hand, the predominant role of individual host factors could explain this phenomenon.

This study has several strengths and limitations. All analysed data were gathered prospectively in the framework of the Swiss Transplant Cohort Study, a representative study covering 93% of all solid organ transplantations in Switzerland (8). The majority of previous studies, which included limited information on infections after re-LTpx, were retrospective. On one hand, the relatively small study size of 60 individuals limits the possibility of in-depth analysis of the study population or extensive correction of patient characteristics in multivariable analyses. On the other hand, the 60 patients had a total of 343 ID events, allowing to study several characteristics of ID events, such as pathogen type and infection site. We could not perform analyses on the role of maintenance immunosuppression due to a lack of granularity of this information within our cohort. In addition, the predominance of Caucasian men in the present study might limit the generalizability of the results.

Given the relevance of infections for patient survival after re-LTpx, future studies seem warranted to further assess the hazard of infections after re-LTpx.

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Conflicts of interest

KK, DN, HHH, PM, KB, CH, CG, RK, NJM report no conflicts of interest.

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List of Abbreviations

CMV: Cytomegalovirus
FLTpx: First liver transplantation
HCV: Hepatitis C
HR: Hazard ratio
HRQoL: health-related quality of life
ID events: Infectious disease events
MELD: Model for end-stage liver disease
Re-LTpx: liver re-transplantation
STCS: Swiss Transplant Cohort Study

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Tables and Figures

Figure 1: Flow chart to illustrate the selection of the study population: Of all patients who received a re-LTpx, patients without information about the FLTpx or re-LTpx due to a primary nonfunctioning graft were excluded from analysis.

Figure 2: Time-line of all patients included in the study population. Each horizontal line corresponds to one patient. Observation time starts with the FLTpx and ends with the last follow-up information. All ID events are indicated: bacterial (orange), viral (blue), fungal (green) and unidentified (purple) pathogens. The time points of the transplantations are indicated by crosses (light blue: FLTpx, red: re-LTpx, dark blue: third transplantation). Death is indicated with a black cross.

Figure 3: Time to event analysis for infectious disease events: comparing ID events after FLTpx and after re-LTpx. 1) Time to the first ID event, 2) Modelling recurrent events.

Table 1

Total		**60**
Gender	male, n (%)	39 (65.0%)
	female, n (%)	21 (35.0%)
Ethnicity	Caucasian, n (%)	56 (93.3%)
	Asian, n (%)	3 (5.0%)
	African, n (%)	1 (1.7%)
Age at 1st transplantation	median (range)	56.0 (18.0-70.0)
Body mass index baseline	median (range)	23.4 (16.7-35.0)
STCS center	Zurich, n (%)	37 (61.7%)
	Berne, n (%)	16 (26.7%)
	Geneva, n (%)	7 (11.7%)
Transplantation		
Time between FLTpx and re-LTpx	years, median (range)	0.7 (0.0-10.6)
Reason for 1st Tpx	Hepatitis C (n, %)	16 (17.6%)
	Hepatocellular carcinoma (n, %)	7 (7.7%)
	Hepatitis B, B-D (n, %)	5 (5.5%)
	Primary sclerosing cholangitis (n, %)	3 (3.3%)
	Primary biliary cholangitis (n, %)	4 (4.4%)
	Alcohol (n, %)	4 (4.4%)
	Idiopathic (n, %)	3 (3.3%)
	Cholangiocarcinoma (n, %)	3 (3.3%)

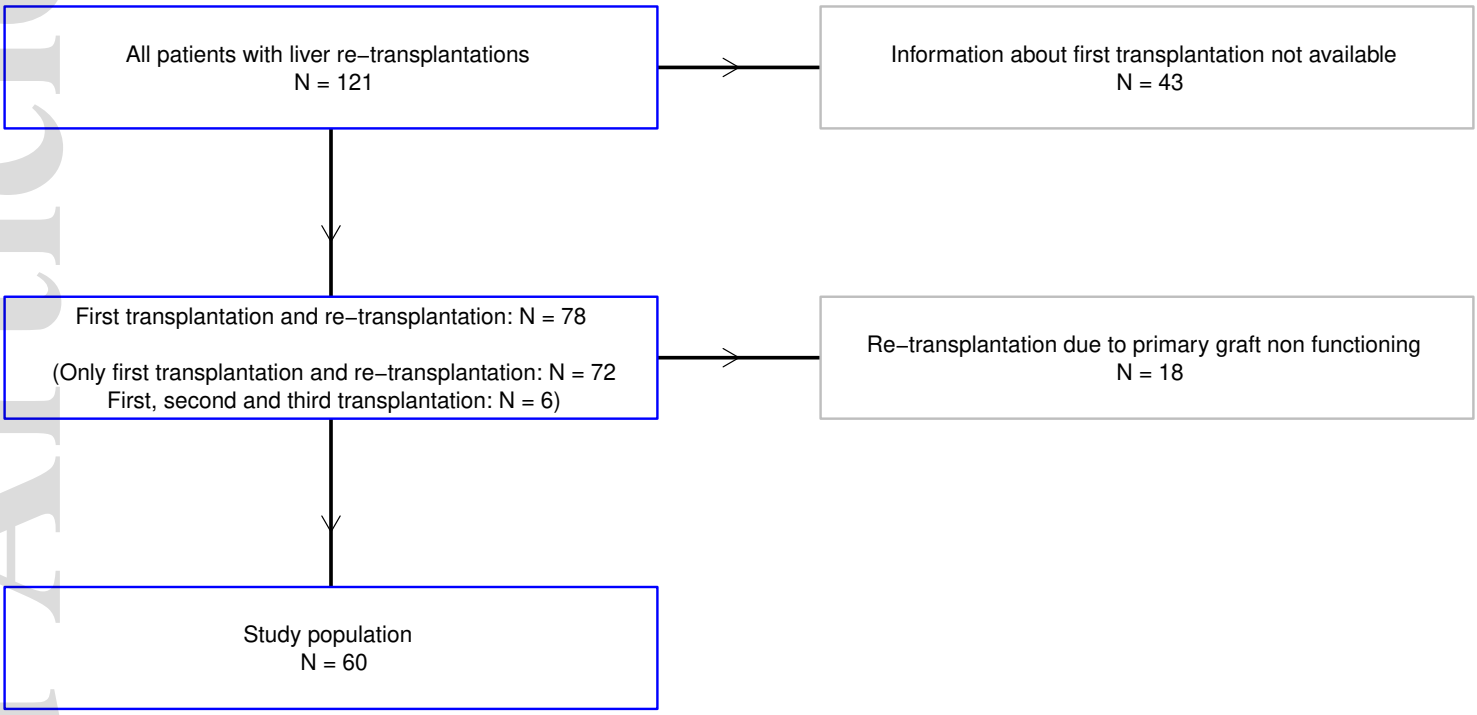
	Autoimmune hepatitis (n, %)	3 (3.3%)		
	Other or unknown (n, %)	12 (13.2%)		
Reason for Re-tpx	Chronic cholestasis (n, %)	15 (16.5%)		
	Primary sclerosing cholangitis (n, %)	4 (4.4%)		
	Ischemic hepatopathy (n, %)	13 (14.3%)		
	Hepatitis C (n, %)	2 (2.2%)		
	Chronic rejection (n, %)	5 (5.5%)		
	Primary biliary cholangitis (n, %)	1 (1.1%)		
	Other or unknown (n, %)	20 (22.0%)		
		FTpx	**Re-Tpx**	**P value**
Donor type	Brain dead, n (%)	39 (65.0%)	54 (90.0%)	0.001
	Living related, n (%)	6 (10.0%)	0 (0.0%)	
	Living unrelated, n (%)	7 (11.7%)	0 (0.0%)	
	NHBD, n (%)	8 (13.3%)	6 (10.0%)	
Liver transplant type	Whole liver, n (%)	44 (73.3%)	59 (98.3%)	< 0.001
	Split liver, n (%)	15 (25.0%)	1 (1.7%)	
Duration of transplant surgery (hours)	median (range)	6.8 (3.0-12.1)	5.4 (2.4-12.9)	0.048
Delayed graft function	n (%)	8 (14.0%)	2 (3.8%)	0.098
MELD score	median (range)	15.0 (6.0-40.0)	24.0 (7.0-40.0)	< 0.001
CHILD score	median (range)	7.0 (5.0-15.0)	8.0 (5.0-14.0)	0.012
Induction immunosuppression	Basiliximab, n (%)	42 (70.0%)	37 (61.7%)	0.44

	No, n (%)	18 (30.0%)	23 (38.3%)	
Hepato-renal syndrome	No, n (%)	46 (76.7%)	35 (58.3%)	0.019
	Yes, no RRT, n (%)	10 (16.7%)	8 (13.3%)	
	Yes, RRT, n (%)	4 (6.7%)	16 (26.7%)	
Biopsy proven rejection	n (%)	17 (28.3%)	12 (20.0%)	0.394
Postoperative complications	Arterial thrombosis, n (%)	15 (25.0%)	1 (1.7%)	< 0.001
	Biliary leak, n (%)	3 (5.0%)	3 (5.0%)	1
	Biliary stenosis, n (%)	15 (25.0%)	5 (8.3%)	0.027
	Bleeding, n (%)	8 (13.3%)	10 (16.7%)	0.798

Table 1: *Basic demographic and clinical characteristics of the study population.*

NHBD: Non-heart beating donor; RRT: Renal replacement therapy

Selection of the study population



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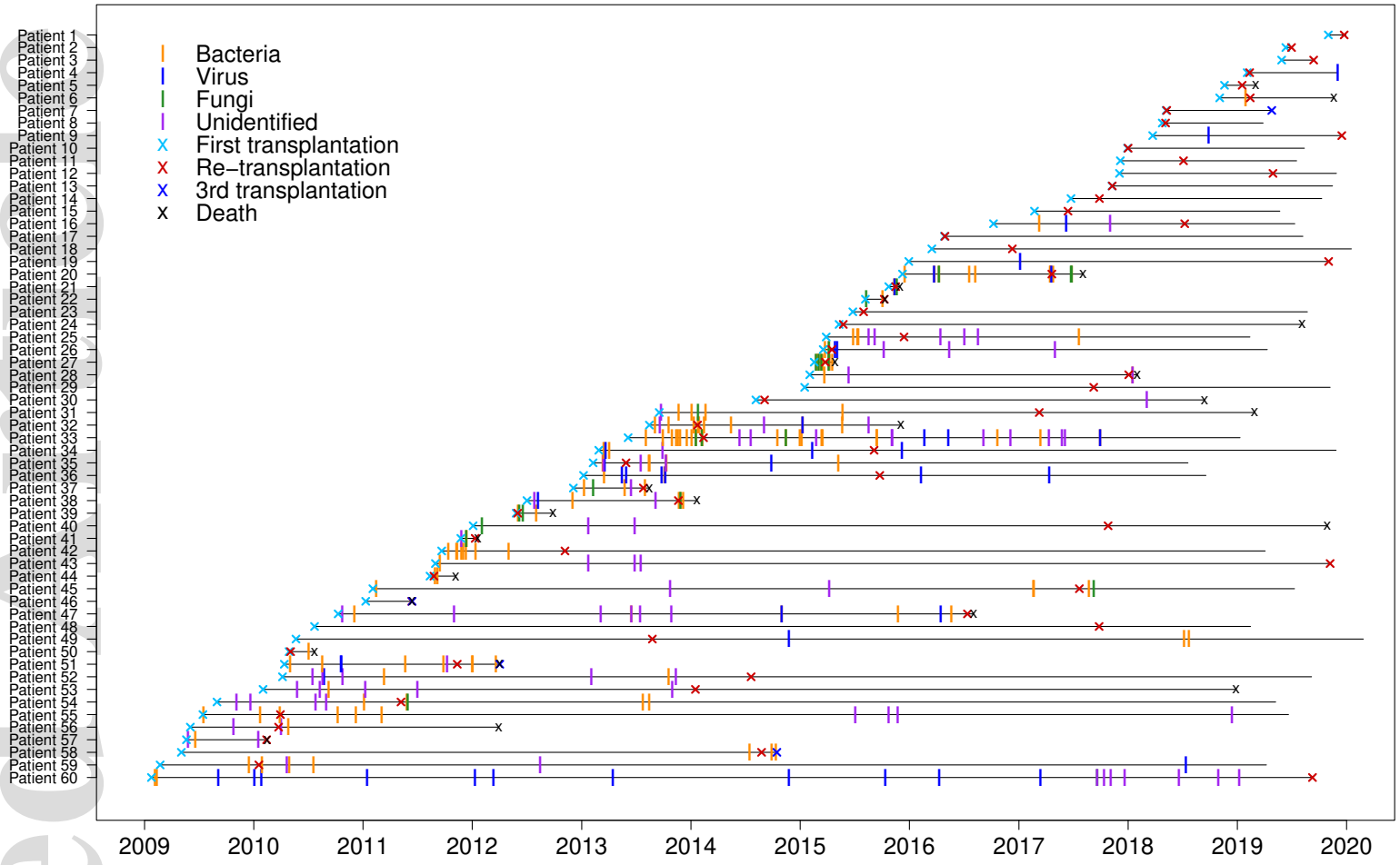

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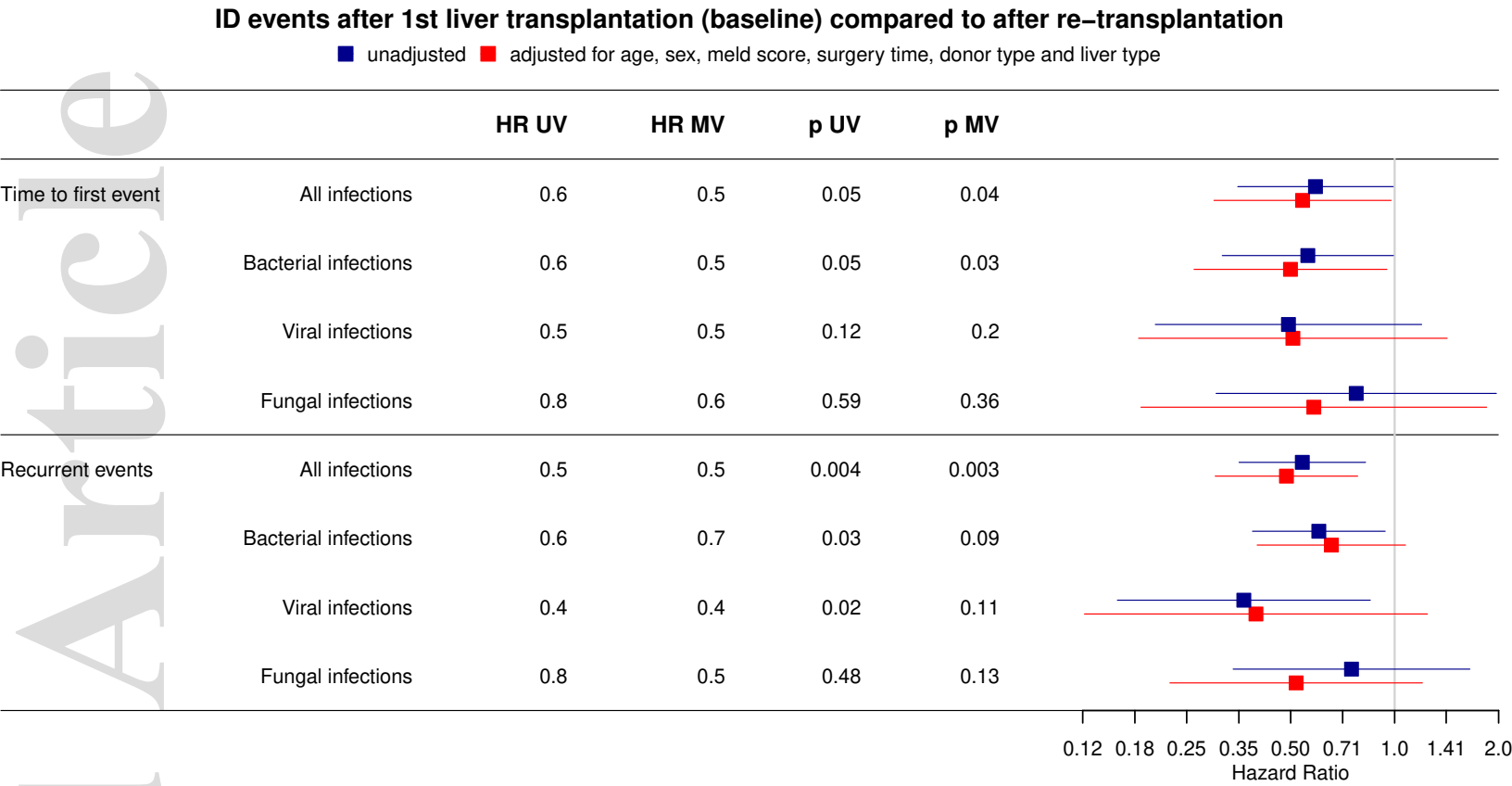

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