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I, Aaron M Delman, hereby submit this original work as part of the requirements for the degree of Master of Science in Clinical and Translational Research.

It is entitled:

Short and Long-Term Outcomes Associated with Technical Variant Liver Grafts in Pediatric Liver Transplantation: In-Situ versus Ex-Vivo

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Short and Long-Term Outcomes Associated with Technical Variant Liver Grafts in Pediatric Liver Transplantation: In-Situ versus Ex-Vivo

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Abstract:

Background: Pediatric patients with end-stage liver disease (ESLD) are subjected to increased waitlist morbidity and mortality due to a lack of appropriately sized donor allografts. To combat waitlist mortality, increased utilization of Technical Variant Grafts (TVGs) has been proposed. However, recent literature suggests recipients of ex-vivo reduced allografts experience worse graft survival and postoperative complications than in-situ split allografts. The goal of this study was to determine if there are significant differences between pediatric patients who receive in-situ split and ex-vivo reduced allografts.

Methods: The prospectively maintained pediatric liver transplant database was queried for all TVG recipients between 2015-2020. Baseline patient demographics, clinical characteristics, intra-operative benchmarks, post-operative complications, and survival curves were compared between in-situ and ex-vivo TVG recipients.

Results: In 70 consecutive TVG LT's, 40 (57.1%) received ex-vivo reduced and 30 (42.9%) received in-situ split allografts. Recipients of in-situ split allografts were more likely to be younger ($p<0.01$), shorter ($p=0.04$), weigh less ($p=0.02$), receive a living donation ($p<0.01$), and a left lateral segment graft ($p<0.01$) than ex-vivo reduced recipients. In-situ recipients were exposed to less cold ischemia ($p<0.01$) and warm ischemia ($p<0.01$) time. Despite this, there was no difference in estimated blood loss ($p=0.26$), blood transfusions ($p=0.32$), or postoperative vascular and biliary complications (all $p>0.05$). Furthermore, with a median follow-up of 1010 days, there was no difference in patient or graft survival between cohorts on Kaplan-Meier analysis ($p>0.05$), and ex-vivo reduced allografts were not associated with an increased hazard of death or graft failure on multivariable cox-regression ($p>0.05$).

Conclusion: Ex-vivo reduced allografts have similar intraoperative, postoperative, and long-term survival outcomes as in-situ split allograft recipients. To combat the significant waitlist mortality experienced by pediatric patients with ESLD, transplant physicians and policymakers should encourage the practice of ex-vivo reduction despite the perceived risks of increased allograft ischemic time.

Introduction:

Pediatric patients with end-stage liver disease (ESLD) are subjected to increased waitlist morbidity and mortality due to the lack of appropriately sized donor liver allografts, preferential allocation to adult recipients, and lack of center expertise (1-3). In 2019, over 7% of pediatric donor allografts were allocated to adults, despite pretransplant mortality remaining at 6.9 deaths per 100-waitlist years (3). Children aged less than one-year continue to experience the worst waitlist outcomes of any listed patients, with 12.1 deaths per 100 waitlist-years (3). To combat waitlist mortality, transplant centers have increased support for living donation, and attempted to increase utilization of technical variant grafts (4). While these efforts are promising, only 3.8% of potentially splitable donors were actually used as technical variant grafts (TVG) in the United States (3, 4).

The primary mechanism for increasing availability of organs for the pediatric population, without decreasing organ availability to the adult population, is through increasing the utilization of TVGs (4). Large single-center experiences have demonstrated similar survival outcomes between TVGs and whole liver grafts, however, TVGs have been associated with more postoperative complications (5-12). Moreover, the two distinct surgical techniques utilized to procure TVGs (in-situ split and ex-vivo reduced), have specialized technical requirements and highly variable outcomes (8, 9, 12-14). Furthermore, recent prospective studies have demonstrated worse outcomes with ex-vivo reduced allografts when compared to in-situ split allografts and whole organs, leaving many centers hesitant to increase utilization of TVGs (13).

The goal of this study was to determine if there are significant differences in intraoperative benchmarks, post-operative complications, and survival outcomes between pediatric patients who receive in-situ split allografts and ex-vivo reduced allografts. Clarifying

and quantifying the differences between in-situ split and ex-vivo reduced recipients is important in providing appropriate utilization and allocation of liver allografts for pediatric liver transplant (LT) recipients. Contrary to recent literature, our hypothesis is that recipients of ex-vivo reduced allografts do not experience worse outcomes than in-situ split recipients. Furthermore, the increased utilization of ex-vivo reduced allografts can potentially mitigate pediatric waitlist mortality.

Methods:

The prospectively maintained database containing all pediatric transplant recipients at Cincinnati Children's Hospital Medical Center was queried to identify all isolated liver recipients between January 1st, 2015 – December 31, 2020. Patients who underwent LT utilizing a TVG were included in the study (Figure 1). Exclusion criteria included all recipients of whole liver allografts and multivisceral transplants. Recipients who underwent LT utilizing a TVG from an ex-vivo reduction were classified as "Ex-Vivo" and those who received a TVG from an in-situ split were classified as "In-Situ." Baseline patient demographics, clinical characteristics, intraoperative details, post-operative complications, and survival curves were compared between cohorts. This study was approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board.

Statistical Analysis:

All baseline donor and recipient characteristics were compared between recipients who received Ex-Vivo reduced allografts and In-Situ split allografts. Data was described using mean ± standard deviation for normal distributions and median [interquartile range] for non-parametric

distributions. Comparison of normally distributed variables was completed with the 2-sample t-test, while non-parametric distributions were compared with the Wilcoxon rank-sum test. Comparison of categorical variables was conducted with the chi-square analysis. Differences were considered statistically significant for p-value < 0.05. Patient and graft survival were assessed with Kaplan-Meier estimates, and graft survival was measured as a combined endpoint, defined as time from transplant until a patient's death or allograft failure. Bivariable and multivariable logistic regression models were created to identify risk factors for post-operative complications as well as one-year patient mortality. In addition, Cox-proportional hazards models were constructed to quantify hazard ratios associated with patient and allograft survival. Variables were selected in a backward stepwise fashion and included in the model if p-Value < 0.1. The proportional hazards assumption was assessed with confirming a zero slope in the scaled Schoenfeld residuals over time. All statistical analysis were conducted in JMP PRO version 15.0 (SAS Institute Inc., Cary, NC, 1989-2019) and SAS version 9.4 (SAS Institute Inc., Cary, NC, 1989-2019).

Results:

Patient Population:

A total of 157 pediatric patients underwent LT from January 1st, 2015 – December 31, 2020. 70 (44.6%) of patients received TVGs and were included in the analysis. Baseline patient demographics and clinical characteristics for recipients of all technical variant grafts are in Table 1. Recipients of In-Situ split TVGs were more likely to be younger (1 vs 2, p<0.01), shorter (73.9cm vs 84.3cm, p=0.04), and weigh less at time of transplant (10.8kg vs 12.4kg, p=0.02) than Ex-Vivo reduced recipients (Table 2). There was no difference in recipient sex,

race/ethnicity, final pediatric end-stage liver disease (PELD) score, etiology of liver disease, or medical condition at transplant between groups. Recipients of In-Situ split grafts were more likely to receive a living donation (14 vs 0, $p<0.01$), left lateral segment grafts (83.3% vs 25.0%, $p<0.01$), and allografts from local donors (60.0% vs 15.0%, $p<0.01$) versus a regional or national share.

Perioperative Benchmarks:

Recipients of In-Situ split allografts were exposed to significantly less cold ischemia time (3.3 hours vs 8.7 hours, $p<0.01$) and warm ischemia time (45.6 minutes vs 55.5 minutes, $p< 0.01$) than the ex-vivo reduced cohort (Table 3). Although total ischemic time was decreased in the in-situ split cohort, there was no significant differences in estimated blood loss (2307.4mL vs 4126.9mL, $p=0.26$), packed red blood cell transfusions (11.9mL vs 36.6mL, $p=0.32$), crystalloid infusions (1273.2mL vs 2248.8mL, $p=0.09$), or colloid infusions (783.8mL vs 1007.7mL, $p=0.24$).

Technical Considerations and Postoperative Complications:

Recipients of in-situ split allografts and ex-vivo reduced allografts underwent statistically distinct inferior vena cava, hepatic artery, and biliary reconstructions (Table 4). In-situ split recipients were more likely to undergo piggyback cavaplasty reconstruction (76.7% vs 20.0%, $p<0.01$), while ex-vivo reduced allografts were most likely to undergo bicaval reconstruction (72.5% vs 13.3%, $p<0.01$). In-situ recipients were also more likely to undergo arterial reconstruction with a primary microsurgical technique (20.0% vs 0.0%) and less likely to utilize an infrarenal arterial conduit (20.0% vs 35.0%, $p=0.02$). In addition, in-situ split recipients

necessitated a roux-en-Y reconstruction more often than ex-vivo reduced (100.0% vs 81.1%, p<0.01). While the type of graft utilized and reconstruction techniques were distinct between cohorts, there was no difference in the incidence of hepatic vein outflow complications (20.0% vs 20.0%, p=1.0), portal venous complications (10.0% vs 5.0%, p=0.42), arterial complications (10.0% vs 5.0%, p=0.42), or biliary complications (30.0% vs 30.0%, p=1.0). On logistic regression analysis for postoperative hepatic arterial thrombosis, the only factors associated with arterial complications were receiving a living donor (OR: 7.36, 95% CI: 1.10-49.38) and increased donor age (OR: 1.18, 95% CI: 1.04-1.34).

Patient & Allograft Survival:

The ex-vivo reduced cohort experienced similar patient and allograft survival rates as recipients of in-situ split technical variant grafts (Figure 2). There was no difference in 30-day (100.0% vs 97.5%, p=0.38), 90-day (93.3% vs 94.9%, p=0.79), 1-year (85.7% vs 94.1%, p=0.27), or 2-year (81.8% vs 89.3%, p=0.45) patient survival. Similarly, there was no difference in 30-day (96.7% vs 97.5%, p=0.84), 90-day (93.3% vs 94.9%, p=0.79), 1-year (85.7% vs 94.1%, p=0.27), or 2-year (81.8% vs 89.3%, p=0.45) allograft survival. Moreover, on Kaplan-Meier survival analysis there was no difference patient (log-rank p=0.36) or allograft (log-rank p=0.54) survival (Figure 3). Cox-proportional hazards models for patient and graft survival, demonstrated only two variables were significantly associated with poor survival: utilizing an interposition conduit for the portal venous reconstruction (HR: 6.74, 95% CI: 1.66 – 29.32) and a postoperative portal venous thrombosis (HR: 12.10, 95% CI: 2.85-51.38).

Discussion:

In this single-center retrospective review of 70 consecutive technical variant graft LTs, recipients of ex-vivo reduced allografts were subjected to increased cold ischemia time and warm ischemia time but experienced the same rate of postoperative complications and had similar patient and graft survival as those who received in-situ split allografts. These findings, from a high-volume pediatric liver transplant center, are an important contribution to the variable literature surrounding the utilization of technical variant grafts. Importantly, they provide transplant surgeons with the reassurance that although ex-vivo reduced allografts experience longer total ischemic time, this finding does not necessary lead to worse outcomes.

Currently, just above 30% of all pediatric liver transplantations utilize technical variant grafts (15). The promise of technical variant grafts to decrease pediatric waitlist mortality has borne out of there similar survival profile to whole organs (16-20). However, a recent review of TVGs from the European Transplantation Society showed that ex-vivo reduction led to longer cold ischemia times and worse outcomes when compared to in-situ splits (21). In addition, a large single center review in the United States described improved 1-year patient and graft survival with in-situ splitting when compared to ex-vivo reduction (22, 23). Our investigation, while similar in methodology to the previous University of California at San Francisco and University of Pittsburgh experiences, is distinct in that it provides details on a similar number of TVG transplants but over a much smaller, and more recent time period (22, 23).

The management of pediatric LT recipients has evolved significantly over the last twenty years and research-based quality improvement initiatives have led to a decreasing incidence of postoperative complications and improved patient survival (24, 25). The improvements in preoperative decision making and medical optimization, intraoperative management, critical care, and postoperative care may have closed the gap in the differential outcomes initially

reported between in-situ split allografts and ex-vivo reduced grafts (26-29). Although there has been a steady increase in pediatric living donation LT, this has been mirrored by a decrease in deceased donor pediatric liver transplantation (3). Since 2015, the proportion of TVG's that were in-situ split has gradually increased while ex-vivo reduced allografts have gradually decreased (3). The findings of our investigation, coupled with the advances in postoperative survival, provide evidence and confidence to transplant providers that ex-vivo reduction is a safe technique, and should be sought out to decrease waitlist mortality.

Limitations of this study include its single institution design and small sample size. The survival outcomes and incidence of postoperative complications represent those of a high-volume pediatric transplant centers and may not be generalizable to low volume centers. Moreover, given the low incidence of postoperative vascular and biliary complications, this study was underpowered to detect a 5% difference between cohorts. Moving forward, multi-institutional prospective databases should be utilized to compare postoperative complications and survival between in-situ and ex-vivo allograft recipients in the modern era. In addition, to best understand the optimal surgical reconstructions in the pediatric population, the Organ Procurement and Transplantation Network, as well as prospective registries should consider collecting anastomotic details in a more robust and standardized fashion between institutions.

In conclusion, this investigation provides evidence that ex-vivo reduced allografts have similar intraoperative, postoperative, and long-term survival outcomes as in-situ split allograft recipients. To combat the significant waitlist mortality experienced by pediatric patients with End-Stage Liver Disease, transplant physicians and policymakers should encourage the practice of ex-vivo reduction despite the perceived risks of increased allograft ischemic time.

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Figure Legends:

Figure 1: Consort diagram detailing the inclusion criteria and distribution of all pediatric liver transplants at Cincinnati Children's Hospital between January 1st 2015 – December 31, 2020. Abbreviations: LT (Liver Transplant), Ex-Vivo (Ex-Vivo reduced allograft), In-Situ (In-Situ split allograft).

Figure 2: Bar graph detailing the patient and allograft survival outcomes for recipients of In-Situ split and Ex-Vivo reduced allografts. There was no difference experienced at any timepoint post-transplantation between cohorts (all $p>0.05$).

Figure 3: Kaplan-Meier survival curves comparing patient and graft survival between recipients of In-Situ and Ex-Vivo technical variant grafts. There was no difference experienced between cohorts with a median follow-up of 1010 days.

Tables:

Table 1: Baseline Patient Demographics and Clinical Characteristics for all included patients who underwent liver transplantation with a technical variant graft between 2015 – 2020.

Patient demographics & clinical characteristics	**All Pediatric Technical Variant Graft Recipients 2015 – 2020 (n = 70)**
Age, y, mean ± sd	3.0 ± 4.3
Sex, female, n (%)	36 (51.4%)
Race/Ethnicity, n (%)	
White	44 (62.9%)
Black	16 (22.9%)
Hispanic	7 (10.0%)
Multiracial	1 (1.4%)
Asian	1 (1.4%)
Pacific Islander	1 (1.4%)
Weight at transplant, kg, median [IQR]	11.1 [8.2 – 16.3]
Height at transplant, cm, median [IQR]	80.3 [70 – 97.4]
Body Mass Index, mean ± sd	17.9 ± 3.4
PELD at transplant, mean ± sd	12.6 ± 11.2
Primary Etiology of Liver Disease, n (%)	
Biliary Atresia	38 (54.3%)
Malignant Neoplasms	12 (17.1%)
Graft Failure	5 (7.1%)
Metabolic Disorders	4 (5.7%)
Cholestatic Liver Failure	4 (5.7%)
Cirrhosis: Cryptogenic/Autoimmune	2 (2.9%)
Acute Hepatic Necrosis	1 (1.4%)
Other, Liver Failure	4 (5.7%)
Donor Type, living, n (%)	14 (20.0%)
Technical Variant Graft Type, n (%)	
Left Lateral Segment	35 (50.0%)
Left Lobe	34 (48.6%)
Right Trisection	1 (1.4%)
Methodology of split liver, n (%)	
In-Situ Split	30 (42.9%)
Ex-Vivo Reduced	40 (57.1%)
Medical Condition at Transplant, n (%)	
Intensive Care Unit	5 (7.1%)
Hospitalized, non-ICU	19 (27.1%)
Home	46 (65.7%)

Table 2: Comparison of baseline patient demographics and clinical characteristics between recipients of In-Situ split technical variant grafts and Ex-Vivo reduced technical variant grafts

Patient demographics & clinical characteristics	**In-Situ Split**	**Ex-Vivo Reduced**	**p-Value**
Age, y, median [IQR]	1 [0-2]	2 [0-7.8]	< 0.01
Sex, female, n (%)	17 (56.7%)	19 (47.5%)	0.45
Race/Ethnicity, n (%)			0.32
White	20 (66.7%)	24 (60.0%)	
Black	7 (23.3%)	9 (22.5%)	
Hispanic	1 (3.3%)	6 (15.0%)	
Multiracial	0 (0.0%)	1 (2.5%)	
Asian	1 (3.3%)	0 (0.0%)	
Pacific Islander	1 (3.3%)	0 (0.0%)	
Weight at transplant, kg, median [IQR]	10.8 [8.5 – 15.1]	12.4 [7.6 – 25.5]	0.02
Height at transplant, cm, median [IQR]	73.9 [70.4 – 91.8]	84.3 [67.5 – 124.1]	0.04
Body mass index, mean ± sd	18.6 ± 4.3	17.5 ± 4.5	0.19
PELD at transplant, mean ± sd	10.4 ± 11.0	14.3 ± 11.3	0.15
Primary Etiology of Liver Disease, n (%)			0.75
Biliary Atresia	20 (66.7%)	18 (45.0%)	
Malignant Neoplasms	4 (13.3%)	8 (20.0%)	
Graft Failure	2 (6.7%)	3 (7.5%)	
Metabolic Disorders	1 (3.3%)	4 (7.5%)	
Cholestatic Liver Failure	1 (3.3%)	3 (7.5%)	
Cirrhosis: Cryptogenic/Autoimmune	1 (3.3%)	1 (2.5%)	
Acute Hepatic Necrosis	0 (0.0%)	1 (2.5%)	
Other, Liver Failure	1 (3.3%)	3 (7.5%)	
Donor Type, living, n (%)	14 (46.7%)	0 (0.0%))	< 0.01
Technical Variant Graft Type, n (%)			< 0.01
Left Lateral Segment	25 (83.3%)	10 (25.0%)	
Left Lobe	5 (16.7%)	29 (72.5%)	
Right Trisection	0 (0.0%)	1 (2.5%)	
Medical Condition at Transplant, n (%)			0.40
Intensive Care Unit	1 (3.3%)	4 (10.0%)	
Hospitalized, non-ICU	10 (33.3%)	9 (22.5%)	
Home	19 (63.3%)	27 (67.5%)	
Donor age, y, mean ± sd	26.3 ± 8.8	18.4 ± 10.2	< 0.01
Donor sex, female, n (%)	12 (40.0%)	12 (30.0%)	0.38
Share type, n (%)			< 0.01
Local	18 (60.0%)	6 (15.0%)	
Regional	12 (40.0%)	26 (65.0%)	
National	0 (0.0%)	8 (20.0%)	

Table 3: Comparison of perioperative benchmarks between recipients of In-Situ split and Ex-Vivo reduced technical variant grafts.

Perioperative Benchmarks	**In-Situ (n=30)**	**Ex-Vivo (n=40)**	**p-Value**
Cold ischemia time, hours, mean ± sd	3.3 ± 2.5	8.7 ± 2.7	< 0.01
Warm ischemia time, minutes, mean ± sd	45.6 ± 15.3	55.5 ± 13.1	< 0.01
Estimated blood loss, mL, mean ± sd	2307.4 ± 3096.4	4126.9 ± 7589.1	0.26
Crystalloid infusion, mL, mean ± sd	1273.2 ± 964.4	2248.8 ± 2878.4	0.09
Colloid infusion, mL, mean ± sd	783.8 ± 580.4	1007.7 ± 846.4	0.24
Packed red blood cell transfusion, mL, mean ± sd	11.9 ± 40.3	36.6 ± 127.2	0.32

Table 4: Surgical anastomosis types and complications compared between In-Situ and Ex-Vivo technical variant grafts.

	In-Situ (n=30)	Ex-Vivo (n=40)	p-Value
Caval anastomosis, n (%)			< 0.01
Bicaval	4 (13.3%)	29 (72.5%)	
Piggyback Cavaplasty	23 (76.7%)	8 (20.0%)	
Cavocavostomy	3 (10.0%)	3 (7.5%)	
Hepatic vein outflow complication, yes, n (%)	6 (20.0%)	8 (20.0%)	1.0
Portal venous anastomosis, n (%)			0.97
Primary	27 (90.0%)	35 (89.7%)	
Interposition conduit	3 (10.0%)	4 (10.3%)	
Portal venous complication, yes, n (%)	3 (10.0%)	2 (5.0%)	0.42
Arterial anastomosis, n (%)			0.02
Primary	7 (23.3%)	10 (25.0%)	
Donor celiac axis to infrarenal aorta	11 (36.7%)	16 (40.0%)	
Infrarenal aortic conduit	6 (20.0%)	14 (35.0%)	
Primary with microsurgical technique	6 (20.0%)	0 (0.0%)	
Arterial complication, yes, n (%)	3 (10.0%)	2 (5.0%)	0.42
Biliary anastomosis, n (%)			0.01
Primary	0 (0.0%)	7 (18.9%)	
Roux-en-Y	30 (100.0%)	30 (81.1%)	
Biliary complication, yes, n (%)	9 (30.0%)	12 (30.0%)	1.0

Figure 1: Consort diagram detailing the inclusion criteria and distribution of all pediatric liver transplants at Cincinnati Children's Hospital between January 1st 2015 – December 31, 2020. Abbreviations: LT (Liver Transplant), Ex-Vivo (Ex-Vivo reduced allograft), In-Situ (In-Situ split allograft).

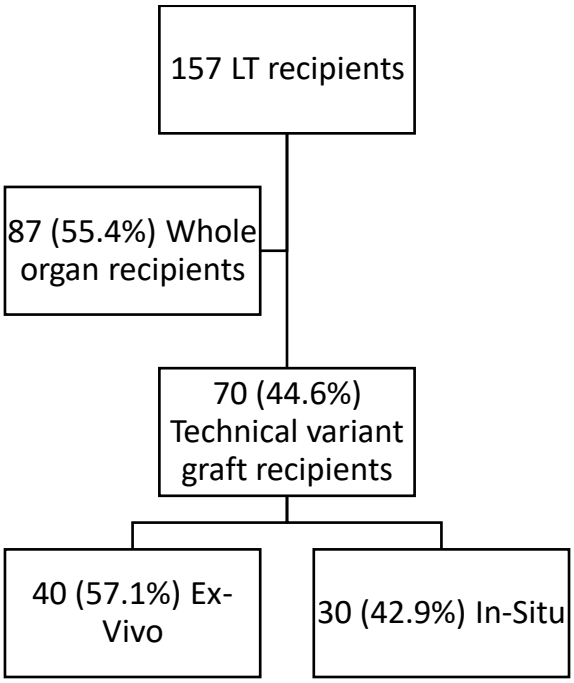

Figure 2: Bar graph detailing the patient and allograft survival outcomes for recipients of In-Situ split and Ex-Vivo reduced allografts. There was no difference experienced at any timepoint post-transplantation between cohorts (all $p>0.05$).

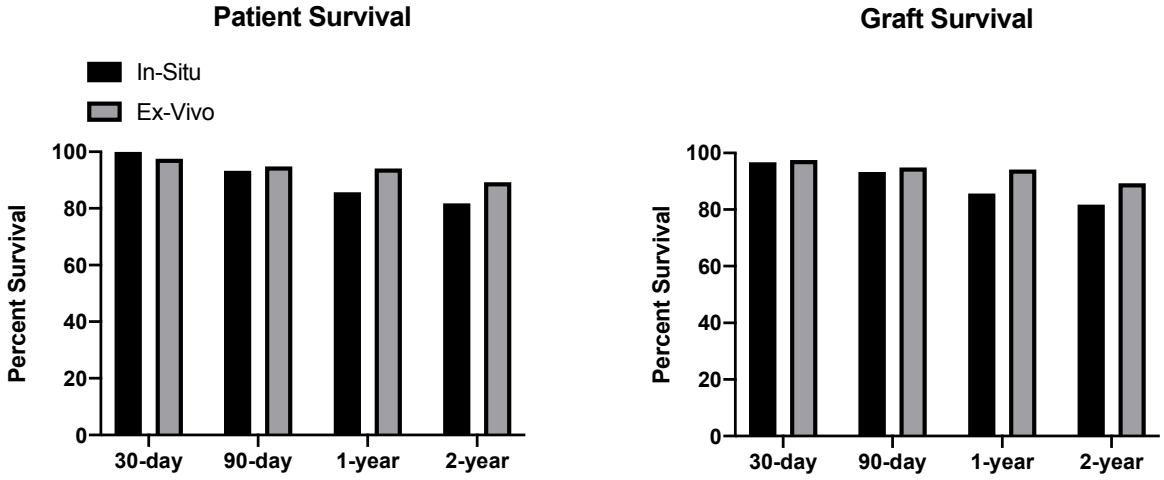

Figure 3: Kaplan-Meier survival curves comparing patient and graft survival between recipients of In-Situ and Ex-Vivo technical variant grafts. There was no difference experienced between cohorts with a median follow-up of 1010 days.