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Enteric Conversion of Bladder-drained Pancreas as a Predictor of Outcomes in Almost 600 Recipients at a Single Center

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Background. Complications associated with bladder-drained pancreata necessitating enteric conversion are common. Data on the outcomes after enteric conversion are conflicting. We studied the association between enteric conversion and the pancreas graft rejection, loss, and mortality. **Methods.** At our center, 1117 pancreas transplants were performed between 2000 and 2016. We analyzed 593 recipients with bladder-drained pancreata, of which 523 received solitary transplants and 70 received simultaneous pancreas-kidney transplants. Kaplan-Meier function was used to estimate time to conversion by transplant type. Cox proportional hazards models were utilized to evaluate patient survival, death-censored graft survival, and acute rejection-free survival while treating conversion as a time-dependent covariate. Subsequently, we examined the association between timing of conversion and the same outcomes in the conversion cohort. **Results.** At 10 y posttransplant, 48.8% of the solitary pancreas recipients and 44.3% of simultaneous pancreas-kidney transplant recipients had undergone enteric conversion. The enteric conversion was associated with 85% increased risk of acute rejection (hazard ratio [HR] = 1.85; 95% confidence interval [CI] = 1.37-2.49; $P < 0.001$). However, the conversion was not associated with graft loss or mortality. In the conversion cohort, a longer interval from engraftment to conversion was associated with an 18% lower rejection rate (HR = 0.82; 95% CI = 0.708-0.960; $P = 0.013$) and a 22% better graft survival (HR = 0.78; 95% CI = 0.646-0.946; $P = 0.01$). **Conclusions.** Enteric conversion was associated with increased risk of rejection, but not increased risks of graft loss or mortality. The decision to convert should consider the increased rejection risk. A longer interval from engraftment to conversion appears favorable.

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Pancreas transplants can be performed in conjunction with a kidney transplant, either simultaneously pancreas-kidney (SPK) or sequentially (pancreas after kidney) in uremic patients with diabetes with results that have consistently improved over the last few decades.[1,2] Currently, SPK is the standard of care for a uremic, nonobese, insulin-dependent recipients with diabetes. Additionally, pancreas-alone transplants are performed in nonuremic insulin-dependent brittle patients with diabetes irrespective of hypoglycemic unawareness status.

Since the first worldwide attempt to cure type 1 diabetes with a whole pancreas transplant at the University of Minnesota on December 17, 1966,[3] there have been over 50 000 pancreas transplants performed worldwide, of which nearly 30 000 have been performed in the United States. Although the majority of pancreas transplants are performed in combination with a kidney,[2] about 10%–20% are still performed as solitary pancreas transplants.

Management of exocrine drainage of the pancreas has evolved. In the 1960s and 1970s, enteric drainage was the

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preferred method of exocrine management. Since the advent of bladder drainage in the early 1980s,[4,5] it became the preferred method across the country, including at the University of Minnesota. Bladder drainage of exocrine secretion offered the advantage of monitoring urinary amylase for early diagnosis of rejection.[1,6] This diagnostic advantage was particularly crucial in solitary pancreas transplants because of the lack of simultaneous kidney to monitor for rejection closely. In the mid-1990s, with the increased use of tacrolimus/mycophenolate-based immunosuppression, pancreas rejection rates decreased remarkably. Moreover, it became apparent that bladder drainage was associated with long-term consequences. The consequences included metabolic derangements such as acidosis and dehydration, urologic complications such as bladder calculi, hemorrhagic cystitis, and recurrent urinary tract infections.[7–10]

For these reasons, the utilization of bladder drainage has declined over the years. From our Scientific Registry of Transplant Recipients analysis[11] of early pancreas graft losses, we noted that bladder drainage accounted for 93% of duct management between 1985 and 1994, which declined to 29% between 1996 and 2005. It further declined to 8% between 2006 and 2018. Nonetheless, bladder drainage may be useful under certain surgical, anatomical, or graft-quality related circumstances.

While some of the bladder exocrine drainage complications can be managed conservatively, many will necessitate enteric conversion. Enteric conversion can effectively resolve 95% of the complications requiring conversion.[7,12]

Despite the frequent use of the enteric conversion procedure to treat the complications associated with bladder-drained pancreas transplants, it is unclear what, if any, other posttransplant health outcomes are affected by the conversion. Based on anecdotal experience, we hypothesized that the rate of rejection would be increased following enteric conversion, but patient and graft survival would be unaffected. To test this hypothesis, we analyzed the long-standing University of Minnesota transplant database to answer the following: does enteric conversion increase the risks of pancreas graft rejection, graft loss, or death following conversion?

Although enteric drainage is the current technique of choice, bladder drainage accounts for nearly 9% of all duct management in the modern era.[11] Therefore, a large cohort of bladder-drained recipients currently exist and will likely need enteric conversion in the future. In a recent publication, our group reported a conversion rate of approximately 30% by 5 y from engraftment.[13] For informed consent, it is crucial to discuss the potential risks associated with the procedure.

MATERIALS AND METHODS

Patient Population

At the University of Minnesota, 1117 pancreas transplants were performed between 2000 and 2016. Of these pancreas transplants, 643 had bladder drainage for exocrine management. The vast majority of the bladder-drained pancreata were solitary transplants n = 568, whereas SPK transplants accounted for 75 of the bladder-drained transplants. For those with multiple pancreas transplants since 2000, the most recent transplant was utilized. Our final cohort consisted of 593 unique recipients with bladder-drained pancreata. Of these, 523 recipients had solitary transplants, and 70 recipients had SPK transplants (Figure 1). Also, we separately analyzed a subset, conversion cohort, of those who underwent conversion n = 202, with the conversion being considered as the baseline or the starting point of follow-up. The basic demographics, immunosuppressant medications, and HLA mismatches were analyzed. The data were available through the University of Minnesota long-standing solid organ transplant database. The database was exempt by the University of Minnesota Internal Review Board (STUDY00000103).

Immunosuppression

Depletional antibody was used for induction, followed by maintenance with a calcineurin inhibitor (CNI; cyclosporine or tacrolimus) plus mycophenolate. Mammalian target of rapamycin (mTOR) inhibitors or rarely azathioprine was used when mycophenolate was not tolerated. Early steroid withdrawal was systemically applied in the early 2000s.

Acute pancreas rejection at the University of Minnesota is typically treated with T-cell-depleting agent. Rabbit thymocyte globulin (7.5 mg/kg in divided doses) is the most commonly used agent. For those who do not mount lymphocyte depletion, due to previous exposure or other reasons, we offer either anti-thymocyte globulin equine preparation or alemtuzumab salvage therapy. On rare occasions, 3 doses of solumedrol 500 mg each may be used if depletional agents are contraindicated. With the Banff introduction of pancreas antibody-mediated rejection,[14,15] we adopted plasmapheresis and intravenous immunoglobulin with or without rituximab to treat biopsy-proven antibody-mediated rejection of pancreas allografts.

Enteric Conversion Indication

In our institution, 202 patients underwent conversion. The leading cause for conversion was cystitis with or without isolated organisms accounting for 50% of cases (n = 100). Hemorrhagic cystitis 15% (n = 31) and acidosis with severe recurrent volume depletion 13% (n = 27) were the second and third leading indications. Other indications included reflux pancreatitis (n = 13) 7% and leaks (n = 9) 5%. We were not able to clearly delineate the indication for conversion in 22 patients or 10% of the cases (Figure 2).

Outcomes of Interest

Acute rejection, graft loss, and recipient mortality were the primary outcomes of this analysis. Acute rejection events were identified in the database in those who received the University of Minnesota standard pancreas rejection treatment based on biopsy-proven findings or clinical diagnosis. Graft loss and death were identified in the database, as reported to the Organ Procurement and Transplantation Network.

Surgical Technique and Complications

Through a midline incision, the lower abdomen is explored down to the dome of the bladder, the usual site of the doudenocystostomy. The doudenocystostomy is taken down by electrocautery, and the bladder is inspected and repaired in 2 layers with running 4-0 polydioxanone suture. The first loop of jejunum that can reach to the pancreas graft duodenum without tension is selected for enteric drainage. The graft duodenum is anastomosed to the proximal recipient jejunum in a side to side, hand-sewn 2-layered fashion. Peritoneal irrigation is then completed, and the abdomen is closed in the standard fashion.

The procedure is mostly well tolerated with a median length of stay of 8 d (interquartile range [IQR] = 7–12 d).

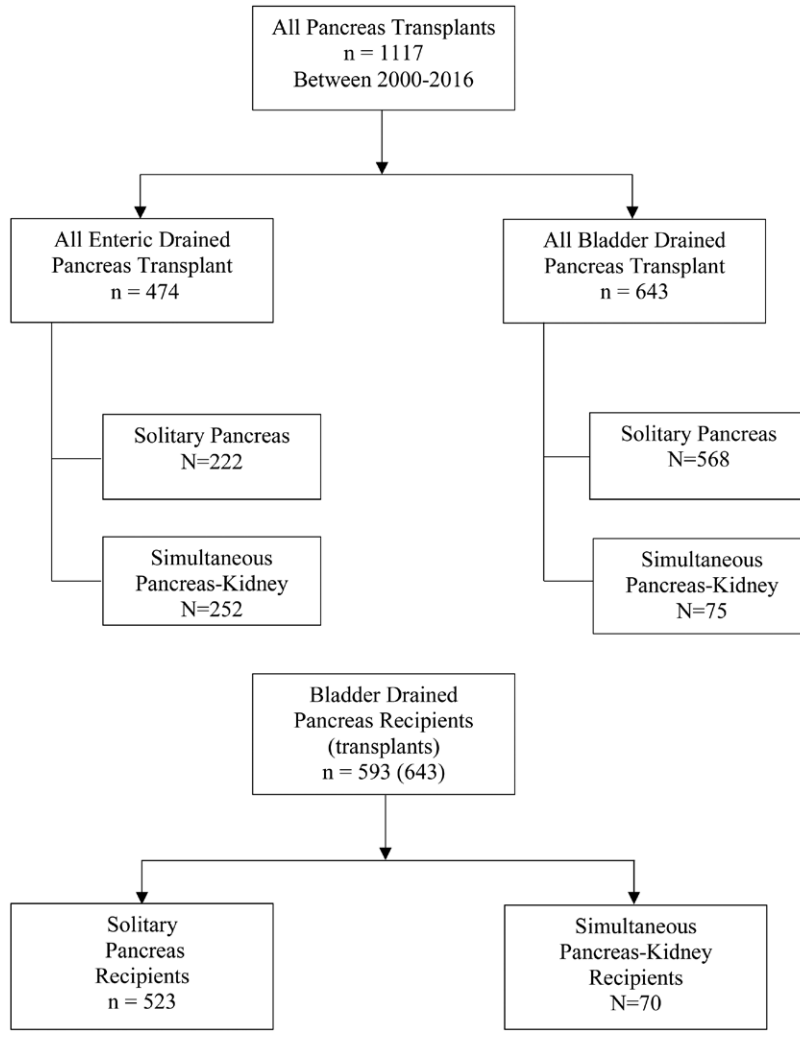

FIGURE 1. Study population.

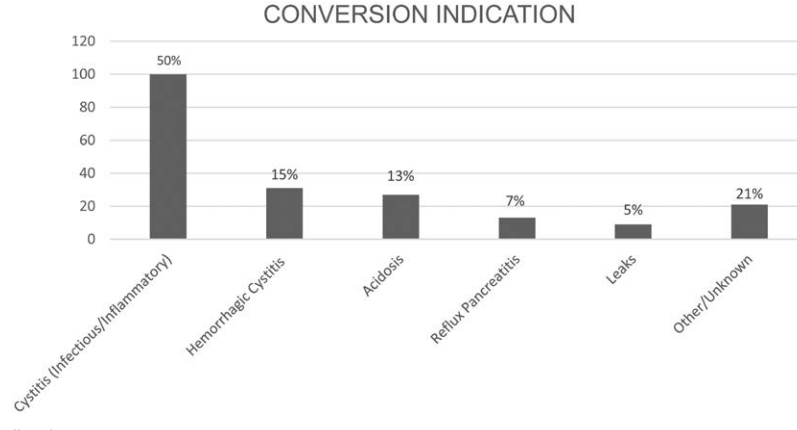

FIGURE 2. Conversion indication.

Surgery-related bleeding occurred in 4 patients (2%), out of which 1 required reoperation. Ileus occurred in 10 patients (5%) and was managed medically. Ten patients (5%) had an anastomotic leak after the conversion of which 7 required reoperation, and 3 were managed with drain placement by interventional radiology means. Pancreatitis without rejection occurred in 4 patients (2%).

Statistical Analysis

In order to examine posttransplant enteric conversion, we first examined the cumulative incidence of enteric conversion over time (Figure 3). Graft failure was defined as complete loss of function and was death censored, and acute rejection was censored at the time of graft failure or death. Following this, multivariate models were analyzed

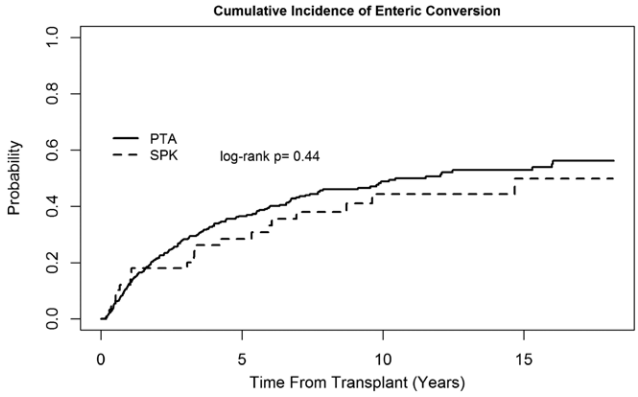

FIGURE 3. Cumulative incidence of enteric conversion by transplant category. PTA, pancreas transplant alone; SPK, simultaneous pancreas-kidney.

for mortality, death-censored graft survival, and acute rejection using enteric conversion as a time-dependent variable. Additional fixed covariates were as follows: age at transplant, gender, retransplant, number of HLA mismatches, and CNI-free status, mTOR inhibitors, and mycophenolate mofetil.

Separately, we analyzed the conversion cohort (n = 202) to examine the association between the timing of conversion and outcomes of interest. The cumulative incidence of patient, graft, and acute rejection-free survival was compared between solitary pancreas and SPK recipients and was not statistically different. Kaplan-Meier curves for patient, graft, and acute rejection-free survival postconversion were created for both the cohort overall (Figure 4) and stratified by timing of conversion, within 1 y of transplant and after 1 y (Figure 5). A separate set of multivariate models was considered for death, graft loss, and acute rejection in the conversion cohort. These models were adjusted for age at conversion, historic rejection before conversion, gender, retransplant status, HLA mismatches, and creatinine at conversion. Statistical analysis and graphics were performed in R version 3.6.0.

RESULTS

Univariate Outcomes

The cumulative incidence of enteric conversion for solitary pancreas transplants was 12.5%, 36.6%, and 48.8% at 1, 5, and 10 y posttransplant, respectively. For SPK, the 1-, 5-, and 10-y cumulative incidences were 12.1%, 28.4%, and 44.3%, respectively (Figure 3).

Median age at transplant was 48.7 y with IQR of (36.7–49.6), males 49.7% and females were nearly equally represented. Of the 593 were recipients, 88.2% had solitary pancreas transplants. CNI containing regimen was identified in 64.8% of the recipients, 53.8% were on a mycophenolate-based regimen, and only ≈7% were on mTOR containing regimens (Table 1).

In the conversion cohort (Table 2), the median time between transplant and conversion was 1.98 y with IQR of 0.8–4.42. Eighteen percent of the group had historic rejection before conversion. Forty-eight percent were males. Solitary pancreas transplants accounted for 89.1% of all enteric conversions. Of the conversion cohort (19.8%) were re-transplant recipients.

Among the participants who underwent enteric conversion with functioning kidneys and not on dialysis, creatinine values were compared before and after conversion using a paired

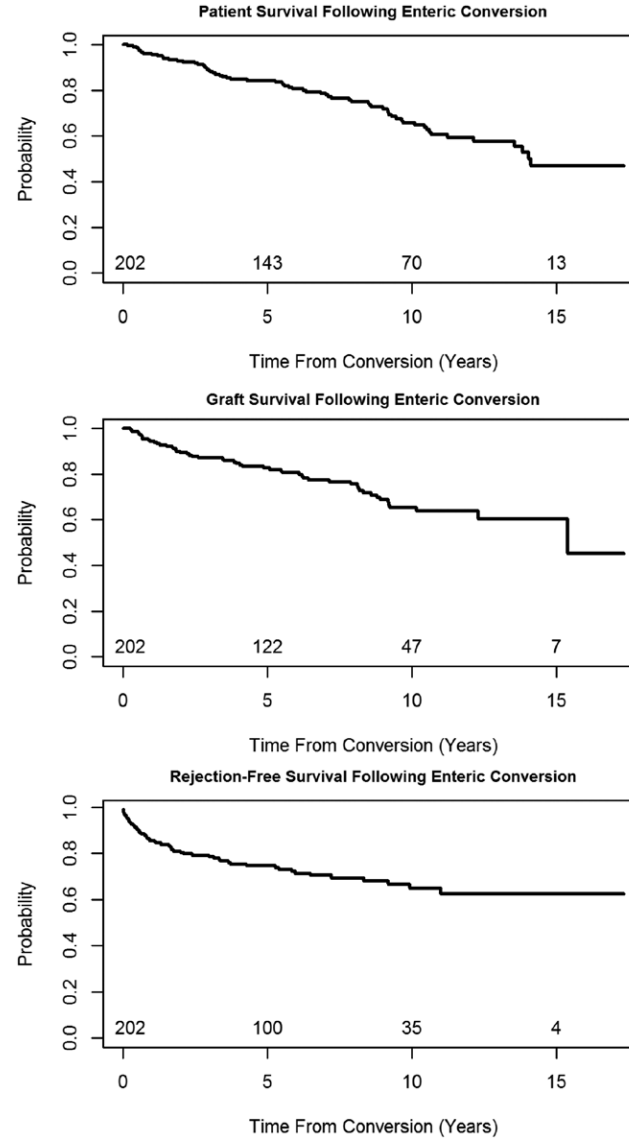

FIGURE 4. Probability of patient survival, graft survival, and acute rejection-free survival.

t test. The mean creatinine following conversion was 0.12 mg/dL lower (95% confidence interval [CI] = −0.19 to −0.06; $P < 0.001$). These results are consistent with slightly improved renal functions after conversion.

In the entire conversion group (Figure 4), the probabilities of patient survival were 98.5% and 95.5% by 6 mo and 1 y, respectively. The probabilities of graft loss at 6 mo and 1 y were 98.5% and 94.3%, respectively. Acute rejection-free survival was observed in 90.5% and 85.6% by 6 mo and 1 y, respectively.

Among those who underwent conversion within 1 y (early) compared with >1 y (late) from engraftment (Figure 5), there were no differences in patient survival, graft loss, or rejection-free survival during the entire study follow-up time (log-rank $P = 0.834$, 0.247 and 0.12, respectively).

Within 1 y from conversion, rejection rates were 18.5% in the early conversion group and 12.6% in the late conversion. Observed graft loss rates were similar in the early and late conversion groups 5.1% and 5.9%, respectively.

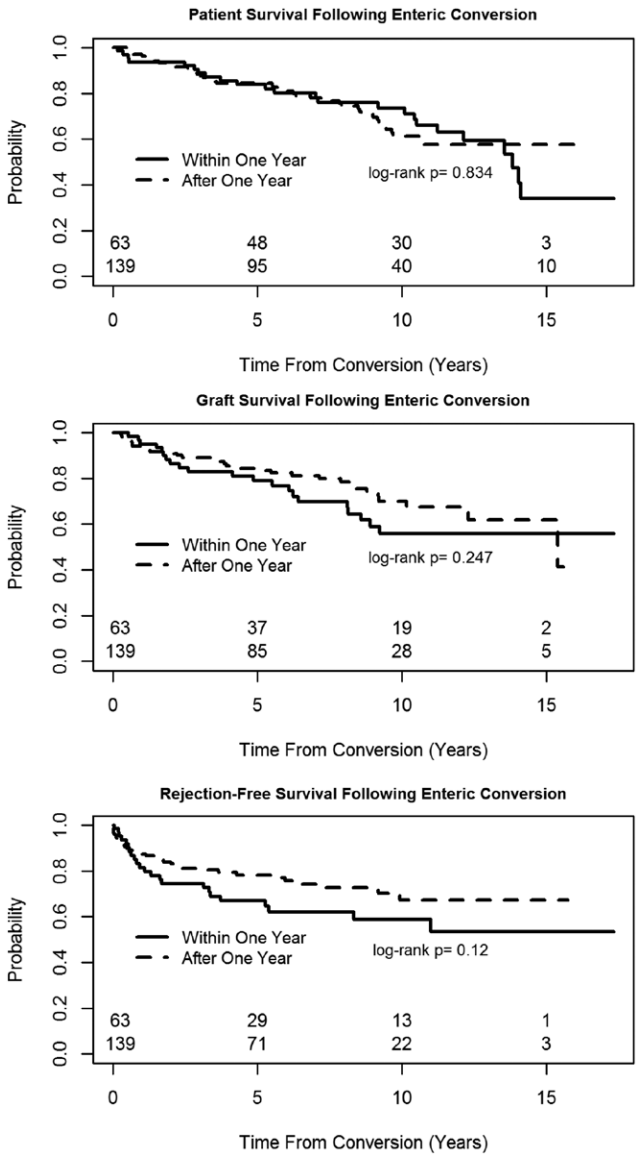

FIGURE 5. Probability of patient survival, graft survival, and acute rejection-free survival stratified by conversion timing.

TABLE 1.

Baseline characteristics of recipients at time of conversion

	Full cohort N = 593
Age at transplant (IQR)	43.7 (36.7–49.6)
Gender (male)	295 (49.7%)
Solitary pancreas	523 (88.2%)
Simultaneous pancreas and kidney	70 (11.8%)
Retransplants	136 (22.9%)
HLA mismatches (IQR)	3.00 (2.75–4.00)
CNI containing maintenance	384 (64.8%)
mTOR inhibitors containing maintenance	42 (7.08%)
Mycophenolate containing maintenance	319 (53.8%)
Peak PRA (IQR)	2.00 (0.00–38.0)
Creatinine median (IQR)	1.31 (0.99–1.71)

CNI, calcineurin inhibitor; IQR, interquartile range; mTOR, mammalian target of rapamycin; PRA, panel reactive antibody.

TABLE 2.

Baseline characteristics of conversion cohort

	Conversion cohort N = 202
Age at conversion (IQR)	47.1 (41.5–54.4)
Time from transplant to conversion (IQR)	1.98 (0.80–4.42)
Rejection before conversion	37 (18.3%)
Gender (male)	97 (48.0%)
Solitary pancreas	180 (89.1%)
Simultaneous pancreas and kidney	22 (10.9%)
Retransplants	40 (19.8%)
HLA mismatches (IQR)	3.00 (3.00–4.00)
Peak PRA (IQR)	2.00 (0.00–23.0)
Creatinine median (IQR)	1.40 (1.20–1.79)

IQR, interquartile range; PRA, panel reactive antibody.

In the conversion group, we identified the first rejection event following conversion in 56 patients. Of these, 41 were biopsy-proven acute rejections. Thirty-seven events were diagnosed as cellular rejection; 4 events were mixed rejections with cellular and antibody-mediated features. The remaining 15 events were clinically diagnosed.

Multivariate Outcomes

Determinants of Acute Rejection-free Survival

In the full cohort (Table 3), the enteric conversion was associated with 1.85-fold increased risk of rejection (hazard ratio [HR] = 1.85; 95% CI = 1.40-2.57; $P < 0.001$). Each HLA mismatch was associated with 15.7% increased risk of rejection (HR = 1.157; 95% CI = 1.043-1.284; $P < 0.001$). Female gender was associated with 33% increased risk of rejection (HR = 1.33; 95% CI = 1.03-1.71; $P = 0.03$). Older age was associated with decreased risk of rejection. Each year older was associated with 3% less risk of rejection (HR = 0.97; 95% CI = 0.96-0.99; $P < 0.001$).

In the conversion cohort (Table 4), the longer the interval from engraftment to conversion, the lower the risk of rejection. Each additional year from engraftment to conversion was associated with an 18% lower risk of rejection (HR = 0.82; 95% CI = 0.708-0.960; $P = 0.013$). Similar to the full model, older age was associated with modestly reduced risk for rejection, and HLA mismatches were associated with a higher risk for rejection.

Determinants of Death-censored Graft Survival

In the full cohort model (Table 5), the enteric conversion was not associated with death-censored graft survival (HR = 0.98; 95% CI = 0.71-1.37; $P = 0.93$) in the fully adjusted time-dependent Cox proportional hazards model. Recipients who were not on CNI-based regimens had a 59% increased risk of graft loss (HR = 1.59; 95% CI = 1.20–2.09; $P < 0.001$). Older age had modestly decreased risk of graft loss. Each additional year of age was associated with 3% less risk of death-censored graft loss (HR = 0.97; 95% CI = 0.953-0.981; $P < 0.001$). The mTOR inhibitor use was not included in the full cohort model because of a lack of model fit.

In the conversion cohort (Table 6), the longer the interval from engraftment to conversion, the lower the risk of graft failure. There was 12% less risk for death-censored graft loss for each additional year from engraftment to conversion (HR = 0.78; 95% CI = 0.646-0.946; $P < 0.011$). Historic

TABLE 3.

Time-dependent Cox proportional hazards for acute rejection

	Rejection model	
	HR (CI)	*P*
Conversion (yes)	1.846 (1.367-2.492)	<0.001
Age at transplant	0.971 (0.957-0.985)	<0.001
Gender (female)	1.330 (1.033-1.713)	0.027
Retransplant (yes)	1.067 (0.797-1.428)	0.662
HLA mismatches (each)	1.157 (1.043-1.284)	0.006
CNI free (yes)	1.097 (0.829-1.451)	0.519
mTOR inhibitors use (yes)	0.793 (0.457-1.376)	0.410
MMF based (yes)	0.889 (0.675-1.171)	0.403

CI, confidence interval; CNI, calcineurin inhibitor; HR, hazard ratio; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin.

TABLE 4.

Cox proportional hazards for acute rejection (conversion group)

	Rejection model	
	HR (CI)	*P*
Age at conversion	0.958 (0.930-0.988)	0.006
Time before conversion, y	0.824 (0.708-0.960)	0.013
Rejection before conversion	1.309 (0.622-2.757)	0.478
Gender (female)	1.120 (0.627-2.001)	0.701
Retransplant (yes)	0.588 (0.261-1.323)	0.199
HLA mismatches (each)	1.297 (1.027-1.639)	0.029
Creatinine before conversion	1.055 (0.708-1.573)	0.792

CI, confidence interval; HR, hazard ratio.

TABLE 5.

Time-dependent Cox proportional hazards for death-censored graft loss

	Rejection model	
	HR (CI)	*P*
Conversion (yes)	0.984 (0.708-1.369)	0.926
Age at transplant	0.967 (0.953-0.981)	<0.001
Gender (female)	1.090 (0.847-1.402)	0.503
Retransplant (yes)	1.120 (0.841-1.491)	0.439
HLA mismatches (each)	0.918 (0.832-1.014)	0.091
CNI free (yes)	1.587 (1.204-2.091)	0.001
mTOR inhibitors use (yes)	–	–
MMF based (yes)	0.822 (0.625-1.079)	0.158

CI, confidence interval; CNI, calcineurin inhibitor; HR, hazard ratio; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin.

rejection before conversion was associated with a 2.2-fold increased risk of graft loss (HR = 2.272; 95% CI = 1.166-4.427; *P* = 0.016).

Determinants of Patient Mortality

In the full cohort model (Table 7), enteric conversion was not a predictor of mortality (HR = 0.98; 95% CI = 0.73-1.32; *P* = 0.89). Older age at transplantation was associated with increased risk of mortality (HR = 1.026; 95% CI = 1.01-1.04; *P* < 0.0001). Similarly, in the conversion cohort (Table 8), older

TABLE 6.

Cox proportional hazards for graft loss (conversion group)

	Graft loss model	
	HR (CI)	*P*
Age at conversion	0.970 (0.939-1.002)	0.068
Time before conversion, y	0.782 (0.646-0.946)	0.011
Rejection before conversion	2.272 (1.166-4.427)	0.016
Gender (female)	1.327 (0.729-2.414)	0.354
Retransplant (yes)	0.564 (0.234-1.355)	0.200
HLA mismatches (each)	1.217 (0.953-1.554)	0.116
Creatinine before conversion	0.565 (0.295-1.082)	0.085

CI, confidence interval; HR, hazard ratio.

TABLE 7.

Time-dependent Cox proportional hazards for patient mortality

	Mortality model	
	HR (CI)	*P*
Conversion (yes)	0.978 (0.726-1.319)	0.886
Age at transplant	1.026 (1.01-1.042)	0.002
Gender (female)	0.842 (0.643-1.102)	0.210
Retransplant (yes)	1.091 (0.796-1.495)	0.587
HLA mismatches (each)	0.888 (0.801-0.984)	0.023
CNI free (yes)	1.209 (0.89-1.643)	0.225
mTOR inhibitors use (yes)	0.916 (0.543-1.544)	0.741
MMF based (yes)	0.823 (0.607-1.114)	0.208

CI, confidence interval; CNI, calcineurin inhibitor; HR, hazard ratio; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin.

TABLE 8.

Cox proportional hazards for mortality (conversion group)

	Mortality model	
	HR (CI)	*P*
Age at conversion	1.032 (1.003-1.062)	0.030
Time before conversion, y	1.006 (0.911-1.111)	0.901
Rejection before conversion	1.306 (0.667-2.557)	0.435
Gender (female)	0.924 (0.555-1.537)	0.761
Retransplant (yes)	0.706 (0.357-1.395)	0.316
HLA mismatches (each)	0.988 (0.802-1.218)	0.912
Creatinine before conversion	1.213 (0.853-1.725)	0.282

CI, confidence interval; HR, hazard ratio.

age at conversion was associated with a slightly increased risk of mortality. For each additional year of age, there was a 3.2% increased risk of mortality (HR = 1.032; 95% CI = 1.003-1.062; *P* = 0.03).

HLA mismatches were associated with a lower risk of mortality (HR = 0.89; 95% CI = 0.80-0.950; *P* = 0.023) in the full cohort; however, this association was not significant in the conversion-only cohort.

DISCUSSION

To date, this is the largest reported cohort of enteric conversion of bladder-drained pancreas transplants.[7,12,16–19] Our

findings can be summarized as (1) enteric conversion was associated with increased risk of acute rejection; (2) enteric conversion was not associated with risks of graft loss or mortality; and (3) the longer the interval from engraftment to conversion, the lower the risk of rejection and graft loss.

The enteric conversion has been reported to be an efficient way to resolve over 95% of the indicative causes, including dehydration.[7,12] Our study showed lower mean creatinine after conversion—0.12 mg/dL lower (95% CI = −0.19 to −0.06; $P < 0.001$). This change, although modest, indicates the stability of the kidney function following a major abdominal procedure.

In contrast to studies reporting that enteric conversion procedure is associated with minimal risks[7,8,16] or no risk,[19] our results demonstrate an increased risk of rejection but affirm no impact on graft loss or mortality. Historically, de novo enterically drained solitary pancreas transplants had higher rejection rates in the first year postengraftment[20] compared with the bladder-drained transplants (15% versus 5%). Our data suggest that enteric conversion event in bladder-drained pancreas also poses an increased risk of rejection. This increased rejection risk raises the question if enteric drainage, whether performed de novo or as a part of conversion procedure, contributes to an increased immunologic risk.

Choi et al[16] recently reported that enteric conversion was associated with improved graft survival compared with continued bladder drainage. However, there were 17.1% graft losses after conversion. Although not comparing rejection rates to nonconverted recipients, they found that rejection after conversion is a predictor of graft loss. Enteric conversion event after bladder-drained pancreas transplants occurs at different time points; however, this future event was not defined or assigned at the beginning of the cohort and should be accounted for as a time-dependent variable. Choi et al[16] used enteric conversion as a nontime-dependent covariate, which may have resulted in biased graft survival estimates.

Adler et al[19] have reported on enteric conversion in SPK recipients and concluded that enteric conversion was not associated with pancreas graft loss. As our cohort mainly consisted of solitary pancreas transplants, our findings complement and affirm those of Adler et al[19] that enteric conversion is not associated with graft loss. Moreover, our findings highlight the association between conversion and the increased risk of rejection, an important outcome that was not addressed by Adler et al.[19] Contrary to their findings, the longer the interval from engraftment to conversion, the better the outcome.

Although enteric conversion was associated with increased risk of rejection in our cohort, it did not increase the risk of graft failure. This finding needs to be interpreted with caution and does not negate the fact that acute rejection is among the leading causes of graft loss.[21–24] In our cohort, rejection before the conversion was a predictor of graft loss. One of the reasons for lack of association between the conversion and graft loss, despite an increased risk of rejection, may be related to rejection intensity. Most (n = 31/41) of the biopsy-proven rejections in our cohort were graded as mild. Aziz et al[24] had shown that treated mild rejection did not impact pancreas longevity. Dong et al[21] reported on the association between rejection and the pancreas allograft loss. They showed that early 1-y acute rejection was associated with complete and partial loss of the pancreas allograft. Interestingly, rejections beyond 24 mo were not associated with complete loss. In our cohort, the median time to conversion was around 2 y from engraftment, which may have attenuated the association with pancreas allograft loss.

Our results of the increased risk of graft loss in association with CNI-free maintenance in our cohort analysis are validated by our previously published experience.[25] Similar to an earlier observation made by Colling et al,[26] in our analysis, female gender was associated with increased risk for rejection in the model addressing the full cohort. In the conversion cohort, this risk was attenuated and was not a significant predictor. In keeping with Teegen et al[27] analysis, our analysis did not find any association between female gender and graft loss or mortality in any of our models.

Our finding of increased rejection risk after conversion is thought-provoking for many reasons. Importantly, it is a major undesirable outcome that must be discussed during the patient informed consenting process. Furthermore, it invites recipients and providers to explore alternative options when applicable before proceeding with enteric conversion as a solution. Additionally, it calls for further investigation to understand the potential etiologies behind this increased risk of rejection after conversion. As enteric conversion is major abdominal surgery and requires bowel rest, medications absorption can be impaired. Therefore, drug exposure may be lower, which can cause immune activation and potentially subsequent rejection.

In terms of perioperative interventions to improve outcomes, with this new insight of increased rejection after conversion, the role of immunosuppression intensification as part of enteric conversion management should be examined. This intensification can be attained by switching to CNI-based regimen if recipients are not already on it before surgery. Utilizing parenteral routes of administration, such as sublingual or intravenous when possible, or using additional immunosuppressant agents may be reasonable approaches.

Study Limitations

Our analyses should be interpreted with several limitations in mind. Because of the retrospective nature of the study, we could not account for unmeasured confounders. The vast majority of the population in our center is Caucasian; therefore, extrapolating the results to other ethnic groups may be limited. The induction regimens differed over the years; thus, residual effects may have influenced the results. However, the timing from engraftment to conversion was long enough to render these residual effects negligible. While rejection was biopsy proven in the majority of cases, clinical diagnosis was made in some, which may have introduced misclassification bias leading to the attenuated impact of rejection on graft loss. Due to the small number of SPK recipients in the conversion cohort and the lack of outcome differences by transplant type in the univariate analysis, we did not adjust for the transplant type in our models, which adds to the limitations of the study. Finally, drug levels were not available for analysis, which did not allow us to adjust for immunosuppression intensity in our study.

Conclusions

Enteric conversion may increase the risk of acute rejection, but not the risk of allograft loss or mortality. The longer the interval from engraftment to conversion, the better the outcome. Providers and patients should consider these findings

when deciding on enteric conversion surgery. The impact of intensifying the immunosuppression regimens perioperatively, by choosing parenteral routes of administration, switching to a CNI-based regimen, or using additional immunotherapies should be evaluated in future investigations.

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