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Relation between primary graft function and 5-year outcomes of islet allogeneic transplantation in type 1 diabetes: a retrospective cohort study in 1210 participants from the Collaborative Islet Transplant Registry.

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Summary

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All authors had full access to all the data in the study and accept responsibility to submit for publication

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All authors contributed to the interpretation of data and critical revision of the article.

FP is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

Declaration of interests

All authors declare no competing interests.

Background: Allogeneic islet transplantation (IT) is a validated therapy in type 1 diabetes. The mechanisms underlying the decline of islet graft function with time are unclear. We evaluated the distinct relation between primary graft function (PGF) and 5-year IT outcomes.

Methods: This retrospective multi center cohort study enrolled all participants from the Collaborative Islet Transplant Registry, who received IT alone, or after kidney transplantation, between 01/19/1999, and 07/17/2020 with a calculable PGF (exposure of interest), measured 28 days after last islet infusion with a validated composite index of islet graft function (Beta2-score). Primary outcome was cumulative incidence of unsuccessful IT, defined as HbA1c ≥ 7.0% (53 mmol/mol) and/or severe hypoglycemia and/or fasting C-peptide < 0.2 ng/mL. Secondary outcomes were: 1) graft exhaustion (fasting C-peptide < 0.3 ng/mL), 2) inadequate glucose control (HbA1c ≥ 7.0% (53 mmol/mol) and/or severe hypoglycemia), and 3) requirement for exogenous insulin therapy (≥14 consecutive days). Relations between PGF and IT outcomes were explored with a competing risk analysis adjusted for all covariates suspected or known to impact outcomes. A predictive model based on PGF was built and internally validated by using bootstraps resampling method.

Findings: In 39 centers, 1210 patients (712 (59.5%) females, mean age 47 years (SD 11) received a median of 10.8 thousand islet-equivalents per kg of bodyweight (IQR 7.4–13.5). Among them, 211 (17.6%) were islet after kidney recipient; 452 (37.4%) received a single islet infusion and 758 (62.6%) received multiple islet infusions. Mean PGF was 14.3 (SD 8.8). The 5-year cumulative incidence of unsuccessful IT was 70.7% (95%CI 67.2–73.9), and was inversely and linearly related to PGF with adjusted subhazard ratio (sHR) of 0.77 (95% CI 0.72–0.82) per 5 units increase of Beta2-score (p<0.0001). Secondary endpoints were similarly related to PGF. The median C-statistic values of PGF for predicting 5-year cumulative incidences of unsuccessful IT, graft exhaustion, inadequate glucose control, and exogenous insulin therapy were 0.70 (range 0.69–0.71); 0.76 (range 0.74–0.77); 0.65 (range 0.64–0.66); 0.72 (range 0.71–0.73), respectively.

Interpretation: This global multiple center study demonstrated a linear and independent relation between PGF and 5-year clinical outcomes of IT. The main study limitations are its retrospective design and the absence of analysis of complications.

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Introduction

Allogeneic pancreatic islet transplantation (IT) is a validated treatment for type 1 diabetes associated with glycemic lability and severe hypoglycemia episodes, and/or after kidney transplantation for end stage renal disease[1]. This beta-cell replacement strategy currently consists of one or more intra-portal infusions of allogeneic pancreatic islets, aiming to restore regulated endogenous insulin secretion and improve blood glucose control[2]. Advances in islet processing and immunosuppression protocols have led to improved outcomes and increased success rates after IT[3]. One randomized trial[4] and several controlled studies[5–9] comparing IT with intensive insulin therapy, showed better metabolic control and reduced incidence of severe hypoglycemia episodes after IT. Long-term results from several prospective[10–12] and retrospective[9,13–17] cohort studies, showed 48–78% graft survival

(defined as C-peptide ≥ 0.3 ng/mL[3]), up to twenty years after IT, together with improved glycemic control and a significant reduction in severe hypoglycemic episodes[13].

Islet infusions are often repeated to increase the overall mass of transplanted islets. On the other hand, using multiple donors for each recipient limits the development of IT in the context of organ shortage. It also increases the risk of procedure-related complications and of alloimmunization. Furthermore, even when a large number of islets are transplanted, a decline in graft function can be observed with time[3]. The underlying mechanisms remain elusive, and the respective roles of inflammatory, allogeneic, and/or autoimmune response, versus the metabolic exhaustion of an initially suboptimal mass of transplanted islets are unclear.

The prolonged success of IT has been related to the primary graft function (PGF) of transplanted islets[18]. PGF was initially defined as islet graft function measured one month after the last islet infusion with Beta-score[19] (range 0–8), a validated composite index of islet function based on stimulated serum C-peptide, fasting blood glucose, HbA1c and the need for exogenous insulin. In a prospective cohort study, optimal PGF, defined by a Beta-score of 7 or 8, was observed in 18 (64%) out of 28 patients who initially received two or three islet infusions, and was associated in these patients with a Kaplan-Meier estimate of 94% (95%CI 63–99) of graft function, and 43% (95%CI 20–64) of insulin independence at 10 years[10]. This relation between early islet graft function and sustained graft survival has been also suggested in two other cohort studies using the Beta2-score[20], a validated simplified and continuous version of the Beta-score[21,22]. However, none of these single center studies was designed to distinguish the role of PGF from other potential confounding factors that may impact IT outcomes, including the recipient pre-transplant characteristics, total mass of transplanted islets, number of islet infusions, as well as the type of immunosuppression and other adjuvant treatments administered after transplantation. Clarifying the distinct impact of PGF is important for refining beta-cell replacement strategies. Measuring PGF could in particular inform the need for repeating infusions of human islets or other insulin-secreting cells to reach expected outcomes.

Therefore, the primary objective of this study was to explore the distinct relation between PGF and five-year clinical outcomes of IT in a large multicenter cohort. We used the Collaborative Islet Transplant Registry (CITR), which is a comprehensive global registry that compiles all data from most islet transplant programs in North America, Eurasia and Australia[3], allowing the adjustment of the analysis to known potential confounding factors. Our secondary objective was to develop a predictive model of 5-year IT outcomes based on the measurement of primary graft function in the CITR cohort.

Methods

Study design and settings:

This observational cohort study was designed to explore the association of PGF with the 5-year outcomes of islet transplantation. We analyzed available data from the Collaborative Islet Transplant Registry (CITR). The CITR is a single, standardized, worldwide repository of comprehensive human islet transplant data, globally collected since January 1999[23].

This deidentified database includes variables from islet preparation and recipient data from consenting individuals with type 1 diabetes. Participation in CITR is voluntary and requires consent from islet transplant centers and individual islet recipients. As a registry, the requirements for patient enrollment and participation have been obtained per the site's institutional review board and/or country's oversight body for human research. Requirements for participation are overseen by the CITR Coordinating Center to ensure that participating islet transplant centers comply with Good Clinical Practice regarding data collection and submission. Participating transplant centers must provide annual documentation of adherence to their local Institutional Review or Ethics Board requirements. United States (US) centers must assure compliance with the Health Insurance Portability and Accountability Act (HIPAA). This study report followed the Strengthening Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Participants:

We enrolled all participants with type 1 diabetes registered in CITR after an allogeneic islet transplant alone (ITA recipient) to treat severe hypoglycemia episodes and/or impaired hypoglycemia awareness or an islet-after-kidney transplant (IAK recipient) in kidney transplant recipients, who received at least one islet infusion between January 19, 1999, and July 17, 2020 reported to CITR as of August 14, 2020, and for whom PGF could be calculated. Pre-transplant recipient characteristics (age, sex, race, blood type, duration of diabetes, body weight in kg, height in cm, body mass index in kg/m^2, HbA1c (glycated hemoglobin) in %, fasting and stimulated C-peptide in ng/mL, fasting blood glucose in mg/dL, daily needs of exogenous insulin in IU/kg/day, number of severe hypoglycemia episodes defined as hypoglycemia requiring third party intervention to correct, presence of type 1 diabetes-associated autoantibodies) and transplantation characteristics (date of islet transplantation waiting list, date and mass of each islet infusion received per recipient in islet-equivalent (i.e. one islet-equivalent IEQ corresponds to the tissue volume of one spherical islet with a diameter of 150 μm[24]) and in islet-equivalent per kg of bodyweight, number of isolated pancreases received per patient, total islet cell volume transplanted in mL, immunosuppression regimen used) were extracted from the CITR database. We also analyzed follow-up data collected in the CITR, 28 days after islet infusion, and then annually for five years following islet transplantation, including fasting C-peptide, fasting blood glucose, glycated hemoglobin, daily exogenous insulin needs, body weight and severe hypoglycemic episodes that occurred since the previous visit. At each new islet infusion, a new follow-up schedule was established as provided for in the CITR protocol. Of note, the reasons for performing or not performing a supplementary islet infusion (e.g., suboptimal graft function, patient preference, rapid graft failure, etc…) were not captured in the registry.

Exposure and covariates:

The study exposure of interest was the patient's primary islet graft function (PGF) measured at day 28 after the last islet infusion[18]. In the present study, we used the Beta2-score[20] to calculate PGF, since this continuous variable (0 for no beta-cell function) was shown to be more accurate than the original Beta-score[19]. Beta2-score was calculated as previously described[20] based on values of fasting C-peptide (nmol/L), fasting blood glucose (mmol/L),

glycated hemoglobin (%) and daily exogenous insulin needs per kg of patient bodyweight (IU/kg per day), using the following formula:

$$\text{BETA-2 score} = \frac{\left(\begin{array}{l}\sqrt{\text{fasting C-peptide(nmol/L)}}\\ \times (1 - \text{insulin dose[units/kg]})\end{array}\right)}{\begin{array}{l}\text{Fasting plasma glucose(mmol/L)}\\ \times \text{HbA1c(\%)}\end{array}} \times 1000$$

Prespecified covariates included all variables that were available in the database and were suspected or known to impact IT outcome: baseline (pre-transplant) recipient age, sex, baseline body mass index, diabetes duration before transplantation, daily exogenous insulin needs per bodyweight at baseline, baseline fasting C-peptide, number of islet infusions, total islet mass transplanted per kg of bodyweight, total cell volume transplanted, type of recipient (ITA or IAK), and the use of specific immunosuppression agents (interleukin 2 receptor antagonist, TNF alpha antagonist, T-cell depleting agent, calcineurin inhibitor and m-TOR inhibitor).

Outcomes:

Current islet transplantation outcomes were used in this study. The primary study outcome was the cumulative incidence of unsuccessful islet transplantation as defined by the IPITA/EPITA (International Pancreas and Islet Transplant Association / European Pancreas and Islet Transplant Association) Igls 2.0 consensus: with glycated hemoglobin level greater than or equal to 7.0 % (53 mmol/mol) and/or with at least one episode of severe hypoglycemia since the last visit and/or with fasting serum C-peptide secretion less than 0.2 ng/mL[25]. Secondary outcomes were: 1) graft exhaustion defined by fasting C-peptide level inferior to 0.3 ng/mL[3], 2) inadequate glucose control using the Clinical Islet Transplantation (CIT) consortium endpoint[26]: with glycated hemoglobin greater than or equal to 7.0 % (53 mmol/mol) and/or occurrence of at least one episode of severe hypoglycemia since the last visit, and 3) the need for exogenous insulin therapy defined as the administration of exogenous insulin during at least 14 consecutive days.

Statistical analysis, handling of missing values:

Categorical variables were expressed as frequency (percentage). Quantitative variables were expressed as a mean ± standard deviation in cases of normal distribution or median (25^{th} – 75^{th} percentile) otherwise. Normality of distributions was assessed using histograms and the Shapiro-Wilk test.

For each IT unfavorable outcome (unsuccessful IT, graft exhaustion, inadequate glucose control, and the need for exogenous insulin), we estimated the cumulative incidence using the Kalbfleisch and Prentice method[27], considering the day 28 after the last islet infusion as the date of origin (i.e. the day of PGF evaluation), censoring the follow-up to 5-year post PGF evaluation or to the last available follow-up, for loss of follow-up and by treating death or delayed islet re-infusion (defined as an islet infusion performed at least one year after the previous islet infusion) as competing events.

The relationship between PGF (measured with Beta2-score at day 28 after the last islet infusion) and the cumulative incidence of the four islet transplantation outcomes were analyzed using Fine and Gray regression models[28]. The analysis considered day 28 after the last islet infusion as the date of origin and censored follow-up at 5 years post-PGF evaluation, or last available follow-up for patients lost to follow-up. Death and delayed islet re-infusion, were treated as competing events. The Fine and Gray regression models were done both with and without adjustment for prespecified covariates suspected or known to impact islet transplantation outcomes available in the database: baseline (before islet transplantation) recipient age, sex, baseline body mass index, diabetes duration before transplantation, daily exogenous insulin needs per bodyweight at baseline, baseline fasting C-peptide, number of islet infusions, total islet mass transplanted per kg of bodyweight, total cell volume transplanted, type of recipient (ITA or IAK), and the use of specific immunosuppression agents (interleukin 2 receptor antagonist, TNF alpha antagonist, T-cell depleting agent, calcineurin inhibitor and m-TOR inhibitor)

PGF, i.e value of the Beta2-score measured at day 28 after the last islet infusion was calculated with the measure of the daily exogenous insulin needs per kg of bodyweight, fasting C-peptide, fasting blood glucose and HbA1c. PGF was considered calculable when at least one of its components was available, and missing values for these components were imputed. Missing data in Beta2-score components and pre-specified covariates adjustment were handled by multiple imputations using the regression-switching approach (chained equations with m = 60 imputations) using all pre-transplant patients characteristics, transplantation characteristics and Beta2-score components at day 28 after the last islet infusion. The number of imputations was chosen to have a maximal fraction of missing information (FMI)/m <1% in all in the multivariable Fine and Gray regression models. The imputation procedure was performed under the missing-at-random assumption with the predictive mean-matching method for quantitative variables, logistic regression model for binary variables, and ordinal logistic regression for ordered categorical variables. Rubin's rules were used to combine the estimates derived from multiple imputed data sets[29].

The shape of relationship between PGF and each islet transplantation outcomes were investigated after categorization of PGF by quartiles and the proportional hazard assumption was assessed by introducing a time interaction term into the Fine and Gray models. The association of PGF with each islet transplantation outcome was first investigated in the overall study population and then assessed in a sensitivity analysis restricted to the patients with all components of the Beta2-score available at day 28 after the last islet infusion. We also investigated the association of PGF with each IT outcome in recipients with a single vs. multiple islet infusions (to avoid overestimation bias of PGF related to the multiple islet infusion), and in islet transplant alone vs. islet-after-kidney recipients (to avoid overestimation bias of C-peptide and therefore PGF in patients receiving IAK due to a potentially lower renal function), by including the subgroup and interaction term between subgroup and PGF into the multivariable Fine and Gray regression models. Unadjusted and adjusted subhazard (sHR) ratio per 5 unit increase in PGF and using lowest PGF quartiles (PGF < 8) as reference were derived from the Fine and Gray regression models as effect sizes.

We assess the performance of PGF to predict each islet transplantation outcomes in terms of discrimination by calculating the Harrell's C-index of agreement adapted to presence of competing risk[30] in each imputed dataset and by reporting median (range) values across the 60 imputed datasets. We also examined the performance of PGF in term of calibration by comparing mean predicted cumulative incidences (estimated by the univariable Fine and Gray model) to the mean observed cumulative incidences (calculated by the Kalbfleisch and Prentice method) in four risk groups determined by the quartile distributions. To address the overestimation issues in developing prognostic model, we performed an internal validation by using bootstraps resampling method (200 resamples) to correct the C-statistic for overoptimism. Risk prediction charts were built from the univariable model (combined estimates obtained in the 60 imputed data sets.

All statistical tests were performed at the 2-tailed α level of 0.05. Data were analyzed using SAS version 9.4 [SAS Institute Inc., Cary, NC 27513, USA].

Role of the funding source:

There was no direct funding source for this study. The cited funding sources did not affect the intent and understanding of the clinical study and had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit it for publication.

Results

Pre-transplant patient characteristics and transplantation characteristics

A total of 1376 patients were registered in the CITR database after having received at least one islet infusion between January 19, 1999, and July 17, 2020. We excluded from this analysis 15 patients with other forms of diabetes than type 1 diabetes, 50 patients who received a simultaneous islet and kidney transplantation, or kidney-after-islet transplantation, and 101 patients with insufficient data to calculate PGF (Figure 1). Overall, 1210 ITA or IAK, type 1 diabetes recipients were enrolled in the study analysis and had a calculable PGF at day 28 after the last islet infusion, were transplanted with at least one islet infusion and followed for up to 5 years in 39 transplantation centers worldwide (28 in North America, 7 in Europa, 3 in Australia and 1 in Asia). Patients were followed up to 5 years after the last islet infusion for a total follow-up of 4670 patients.years. Among the 1210 patients of the present study, 28 (2.3%) deaths were reported during the follow-up. The baseline pre-transplant patients characteristics, and the characteristics of transplantation are summarized in Table 1. The mean age of the recipients was 47 years old (SD 11) with 712 (59.5%) females and a mean diabetes duration of 30.4 years (SD 11.2) before transplantation.

Prior to transplantation, the median HbA1c was 7.8 % (IQR 7.0–8.8), 731 (71.4%) patients had experienced at least one severe hypoglycemic episode, and the median daily insulin needs was 0.6 IU/kg/day (SD 0.2). Patients were transplanted after a median time of 7.1 months (IQR 2.6–16.1) on the waiting list, alone in 986 (82.4%) recipients or after a kidney

transplantation in 211 (17.6%) recipients. Patients received a median of 2.0 (IQR 1.0–2.0; range 1–5) islet infusions corresponding to a median total islet mass transplanted of 10.8 (IQR 7.4–13.5) thousand islet-equivalents per kg of bodyweight, and a median total islet cell volume transplanted of 5 mL (IQR 3.0–7.5)

Among them, 452 (37.4%) patients received a single islet infusion and 758 (62.6%) received multiple islet infusions, including two, three or at least four infusions in 632 (83%); 119 (16%); 7 (1%) patients, respectively. Out of the recipients who received multiple islet infusions, 528 (70%) received all of their infusions within the first 6 months after their initial infusion. The most frequently used immunosuppressive agents were calcineurin inhibitors, m-TOR inhibitors for maintenance and T-cell depleting agents, interleukin 2 receptor antagonists, and TNF alpha antagonists for induction immunosuppression (Table 1).

Overall, the mean value of PGF, the study exposure, estimated by the Beta2-score calculated at day 28 after the last islet infusion, was 14.3 (SD 8.8). In participants who received a single islet infusion, the mean PGF was 10.1 (SD 7.8), as compared to 16.8 (SD 8.4) in patients who received multiple islet infusions ($p < 0.0001$). ITA recipients had a mean PGF of 13.9 (SD 8.6) and IAK recipients had a mean PGF of 16.2 (SD 9.5) ($p=0.002$). The values of PGF and its individual components before and after imputations are reported in the appendix (p4).

Association between PGF and primary study outcome

In a survival analysis taking into account death and delayed islet re-infusion (see methods) as competing events, 19.6% (95% CI 17.2–22.2) of recipients did not reach IT success 28 days after last islet infusion (Figure 2A). In this specific population, median PGF was 5.0 (IQR 0.6–11.8). The cumulative incidence of recipients who did not reach IT success increased at 1, 3 and 5 years post last islet infusion from 39.9% (95%CI 36.7–43.1), to 59.3% (95%CI 55.8–62.6) and 70.7% (95%CI 67.2–73.9), respectively. The appendix (p5) details the number and percentage of patients who have reached the primary study outcome at each follow-up visit.

After adjustment on prespecified covariates and handling missing values by multiple imputations, PGF was significantly and inversely related to unsuccessful IT with adjusted subhazard ratio (sHR) of 0.77 (95%CI 0.72–0.82) per 5 units increase of Beta2-score ($p<0.0001$) (Figure 3). After categorization of PGF by quartiles, this association appeared linear, resulting in a dose-effect response. Patients who experienced a PGF greater than 20.1 (75^{th} percentile) were associated with lower incidence of unsuccessful IT at 5 years compared to patients with PGF fewer than 8 (25^{th} percentile), with an adjusted sHR of 0.35 (95%CI 0.26–0.45) ($p<0.0001$) (appendix pp6–7).

The independent association between PGF and unsuccessful IT during the 5-year follow-up was further confirmed in sensitivity analyses in various sub groups: single vs. multiple islet infusions recipients (Figure 4A), ITA vs. IAK recipients (Figure 4B) as well as in patients with all PGF components available (complete cases, appendix p2).

As PGF is a composite index, we also analyzed the relationship between each PGF individual components, and the cumulative incidence of unsuccessful islet transplantation in the 5-year follow-up (appendix p3).

Association between PGF and secondary study outcomes:

Similar results were observed with all three secondary study outcomes. Graft exhaustion, inadequate glucose control, and the need for exogenous insulin therapy were observed in 8.8% (95%CI 7.2–10.6), 17.8% (95%CI 15.4–20.2) and 38.2% (95%CI 35.3–41.0) of patients 28 days after the last islet infusion, respectively (Figure 2B–2C–2D). These patients experienced a median PGF of 0 (IQR 0–0.9), 6.7 (IQR 1.8–13.8) and 7.6 (IQR 4.3–11.5) respectively.

The cumulative incidences of graft exhaustion, inadequate glucose control, and need for exogenous insulin therapy at 5 years were 42% (95%CI 38.7–45.3), 67.6% (95%CI 64.2–70.8) and 76.5% (95% CI 73.6–79.1), respectively (Figure 2B–2C–2D). Following adjustment on prespecified covariates, PGF was significantly and inversely related to the cumulative incidence of graft exhaustion, inadequate glucose control and need for exogenous insulin therapy, with adjusted sHR of 0.63 (95%CI 0.57–0.70), 0.80 (95%CI 0.76–0.85) and 0.77 (95%CI 0.73–0.81), respectively (per 5 units increase of Beta2-score; $p<0.0001$) (Figure 3). Similarly, these associations between PGF and the three secondary outcomes were all linear, resulting in a dose-effect response (appendix pp6–7).

The independent association between PGF and all three secondary outcomes during the 5-year follow-up was further confirmed in various subgroups, including single vs. multiple islet infusions recipients (Figure 4A), ITA vs. IAK recipients (Figure 4B), and complete cases (appendix, p 2)

We also analyzed the relationship between each of PGF individual components, and the cumulative incidence of the three secondary study outcomes during the 5-year follow-up (appendix p3).

Details of the multivariable regression models examining the relationship between primary graft function and the 5-year cumulative incidence of the four unfavorable outcomes in islet transplantation are presented in the appendix (pp8–10). Number of islet infusion, total cell volume or islet mass transplanted in the recipients had no significant impact on the four IT unfavorable outcomes in the whole cohort.

IAK recipients showed worse outcomes such as unsuccessful IT, poor glucose control, and the need for exogenous insulin therapy compared to ITA recipients, but there was no significant difference in the incidence of graft exhaustion between these two groups.

Prediction of islet transplantation outcomes

PGF alone was able to predict the probability of cumulative incidence of unsuccessful IT, graft exhaustion, inadequate glucose control, and the need for exogenous insulin therapy during the 5-year follow-up with good accuracy. The median C-statistic values of the

adjusted models were 0.70 (range 0.69–0.71), 0.76 (range 0.74–0.77), 0.65 (range 0.64–0.66) and 0.72 (range 0.71–0.73) respectively (appendix pp11–12).

After internal validation of 200 bootstraps resamples, predictive equation models of the incidence of the four outcomes as a function of PGF were derived. The predicted cumulative incidences of the four outcomes of the study at 2 and 5-year follow-up associated with incremental values of PGF are indicated in Table 2.

Finally, the prediction models developed from the present study were integrated into a software program allowing to display cumulative incidences and median survival of the four IT study outcomes that can be predicted for an individual patient, according to the values of PGF measured simultaneously with glycated hemoglobin, daily exogenous insulin needs, body weight, fasting blood glucose and fasting C-peptide, 28 days after the last infusion. A current version of the calculator is available online (https://lillemodel.shinyapps.io/PGF-islet/).

Discussion

In this retrospective cohort study, we analyzed the relation between early islet graft function and the 5-year clinical outcomes of IT. The results demonstrated an inverse, independent and linear relation between PGF, measured 28 days after last islet infusion and the cumulative 5-year incidence of unfavorable outcomes including unsuccessful IT, graft exhaustion, inadequate glucose control, and the need for exogenous insulin therapy. Our results also suggest that a simple model based on PGF can predict long term IT outcomes with reasonable accuracy.

One key asset of our study was the use of the most comprehensive IT cohort available worldwide, which supports the generalizability of our findings. Our analysis enrolled a total of 1210 type 1 diabetes participants who were transplanted in 39 centers in four continents, using heterogenous allocation systems, patient and islet characteristics, and clinical practices. This unique setting allowed us to distinguish the role of PGF from that of other factors known to impact IT outcomes, including the characteristics of the recipient and transplanted islets, as well as transplantation strategies and immunosuppression regimens.

The distinct impact of early graft function on long-term survival is well established in renal transplantation. Delayed kidney graft function is associated with poor long-term outcome, independently of immunologic factor[31]. In a randomized trial using machine perfusion, increasing the function of the kidney graft by lowering serum creatinine levels in the first two weeks following transplantation led to greater graft survival at one year[32]. In IT, the assessment of early graft function is complicated by the potential repetition of islet infusions. In the present study, we defined PGF as islet graft function measured 28 days after the last infusion, a time sufficient to ensure the restoration of physiological blood flow to the transplanted islets through vascular sprouting[33]. Notably, this allows us to study multiple islet infusions as a single intervention. Several composite indexes have been proposed to measure islet graft function based on simultaneous measurements of serum C-peptide, blood glucose, and the need for exogenous insulin. In the present study, we

measured PGF with the Beta2-score, a simple and continuous variable derived from a single fasting blood sample measured 28 days after the last islet infusion. PGF could be calculated in more than 90% of CITR participants after imputation of missing values. This allowed us to unveil a dose-effect relation between PGF and the retention of IT success, independently of pre-transplant patient characteristics, transplantation strategies, and immunosuppression regimens (appendix pp6–7). Noteworthy, the retention of IT success and other secondary outcomes were not significantly related to the number of infusions received, nor to the overall mass of transplanted islets. These results are aligned with those of a large single-center retrospective study, in which long-term graft survival was not associated to total islet mass but rather to islet graft function between 6 and 12 months[13]. In a prospective cohort study in which recipients deliberately received iterative islet infusions aiming to maximize PGF[10], the median survival of graft function was 10 years (IQR 8–10) among patients who experienced optimal PGF (Beta-Score of 7 or 8) vs. 6.0 years (IQR 1.9–10.0) in those with suboptimal PGF (Beta-score≤6; p=0.018). In a retrospective single center study, higher values of Beta2-score measured 75 days after IT were associated with longer duration of insulin independence[22]. A third study showed that patients who achieved and maintained insulin independence had higher Beta2-score values 7 days after IT than those who remained insulin dependent[21]. Therefore, in line with existing evidence, the present study demonstrated that early function of successfully engrafted islets is essential to maximize islet graft survival, independently from the number of infusions or the total mass of islets transplanted.

Our study has several limitations. First, the study design was retrospective and observational. Overall, 758 (62.6%) patients received multiple islet infusions within 6 months in the present study but the reason for repeating islet infusion was not captured in the registry. One must therefore remain cautious when extrapolating the clinical utility of PGF for guiding the decision of supplementary islet infusion. This will need to be tested in a prospective interventional trial. Furthermore, implementing a deliberate strategy of early, repeated islet infusions to improve PGF may be hindered by limited availability of donor pancreases. It could also make it more difficult to secure reimbursement from healthcare systems in certain countries. Second, we only evaluated efficacy outcomes and not the complications that can occur after IT, such as procedure related adverse events, alloimmunization, or change in kidney function. In addition, the four components used to calculate PGF were all available in 318 (26%) patients, and multiple imputation was necessary to calculate PGF in many patients. However, the mean values of PGF calculated with or without imputation (complete cases) were similar. One cannot exclude that using more sophisticated methods to evaluate islet graft function, such has dynamic tests of insulin secretory reserve, could further refine the prediction of long-term outcomes. It is also possible that evaluating islet graft function at other time points would have been more efficient. In the present study, evaluating PGF with the Beta2-score at day 28 after last infusion allowed a prediction of good accuracy as shown by the C-statistics of the model in the four different study outcomes. Day 28 also appears as a reasonable time in clinical practice. Our analysis was not adjusted on kidney function which could have impacted Beta2-score values by increasing circulating C-peptide levels. However, our sensitivity analysis showed that the significance of PGF was maintained in patients receiving islet transplantation alone, i.e. without a previous kidney transplant.

Finally, this hypothesis-driven analysis was not intended to investigate the specific effect of each pre-specified covariate, but rather to demonstrate the independent relation between PGF and 5-year IT outcomes. In another CITR analysis that was conducted without adjustment to PGF in 398 patients receiving ITA[17], the age of the recipient, the total mass of transplanted islets, and the type of adjuvant anti-inflammatory and immunosuppressive treatments were found to be associated with the overall success of the transplant. Our multivariable analyses also revealed an association between lower pretransplant daily insulin needs and recipient's body mass index, the absence of a previous kidney graft, a longer duration of diabetes, as well as the use of m-TOR inhibitor or TNF alpha antagonist, and favorable results for at least one of the four study outcomes (appendix pp8–10). These confounding factors had, however, a negligible impact on the sHRs of the association between PGF and the outcomes. This explains why our prediction model which was based only on PGF demonstrated good accuracy.

In conclusion, this study conducted in the largest available global cohort of IT recipients demonstrated a linear and inverse independent relation between PGF measured one month after the last islet infusion (Beta2-score at day 28) and the 5-year cumulative incidence of unfavorable IT outcomes. This remarkable association between early graft potency and long-term clinically meaningful outcomes has important clinical implications for beta cell replacement. First, measuring PGF could guide current clinical practice by helping to individualize the decision to repeat islet infusions, independently of a predefined islet mass threshold, according to the expected clinical outcomes, such as insulin independence or disappearance of severe hypoglycemia episodes. Second, PGF could be used as an early and reliable surrogate endpoint of IT success in future clinical trials. Overall, our results indicate that, to improve the outcome of current strategies for beta-cell replacement, more attention should be directed to evaluate and optimize early islet graft potency, i.e. by enhancing the survival and function of transplanted islets or other insulin-secreting cells.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Data sharing

The data underlying the results presented in this article are not publicly available. Deidentified individual participant data, as well as a data dictionary, can be made available

by the CITR to investigation centers that provide a methodologically robust study design and agree to report results from the cohort without stratifying results by investigating center.

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Research in context

Evidence before this study

Beta-cell replacement with allogenic islet transplantation (IT) is a validated treatment for type 1 diabetes associated with glycemic lability and severe hypoglycemia episodes, and/or after kidney transplantation for end stage renal disease. A decline in islet graft function is however often observed with time and the underlying mechanisms remain elusive. We searched in PubMed and Embase databases from Jan. 1, 2000, to Oct. 1, 2022, using the search terms “islet transplantation” AND “long term outcome” AND (“prediction” OR “prognostic”). We found three prospective and six retrospective single center or multicenter studies which reported IT outcomes after at least five years of follow-up. Various variables have been related with favorable long-term outcomes of IT including, the recipient characteristics like age, female gender and low insulin requirements prior to transplantation, the number and/or mass of transplanted islets, and the drugs used for induction and/or maintenance of immunosuppression. Some studies also suggest a tight relation between long term outcome and primary graft function (PGF), measured one month after last infusion with a validated composite index of beta cell function. However, none of these studies were designed to disentangle the role of PGF from other potential confounding factors that may impact long-term outcomes. Clarifying the distinct impact of PGF is important for refining the future use of IT and other beta-cell replacement strategies.

Added value of this study

In the present study, we tested the hypothesis that PGF is an independent predictor of 5-year clinical IT outcomes. For that purpose, we used the Collaborative Islet Transplant Registry (CITR), which is a comprehensive global registry that compiles all data from most islet transplant programs in North America, Eurasia and Australia, allowing the adjustment of the analysis to known potential confounding factors. The results demonstrated an inverse, independent and linear relation between PGF, measured 28 days after last islet infusion and the cumulative 5-year incidence of unfavorable outcomes after IT including unsuccessful IT, graft exhaustion, inadequate glucose control, and the need for exogenous insulin therapy. Our results also suggest that a simple model based on PGF can predict long term IT outcomes with reasonable accuracy.

Implications of all the available evidence

IT is a validated alternative therapy for patients with severe forms of type 1 diabetes. The distinct association demonstrated in the present study between early graft potency and 5-year IT outcomes has important clinical implications for beta-cell replacement. First, measuring PGF could guide current clinical practice by helping to individualize the decision to repeat islet infusions, independently of a predefined islet mass threshold, or the achievement of clinical outcomes such as insulin independence or disappearance of severe hypoglycemia episodes. Second, PGF could be used as an early and reliable surrogate endpoint of IT success in future clinical trials. Overall, our results indicate that, to improve the outcome of current strategies for beta-cell replacement, more attention

should be directed to evaluate and optimize early islet graft potency, i.e. by enhancing the survival and function of transplanted islets or other insulin-secreting cells.

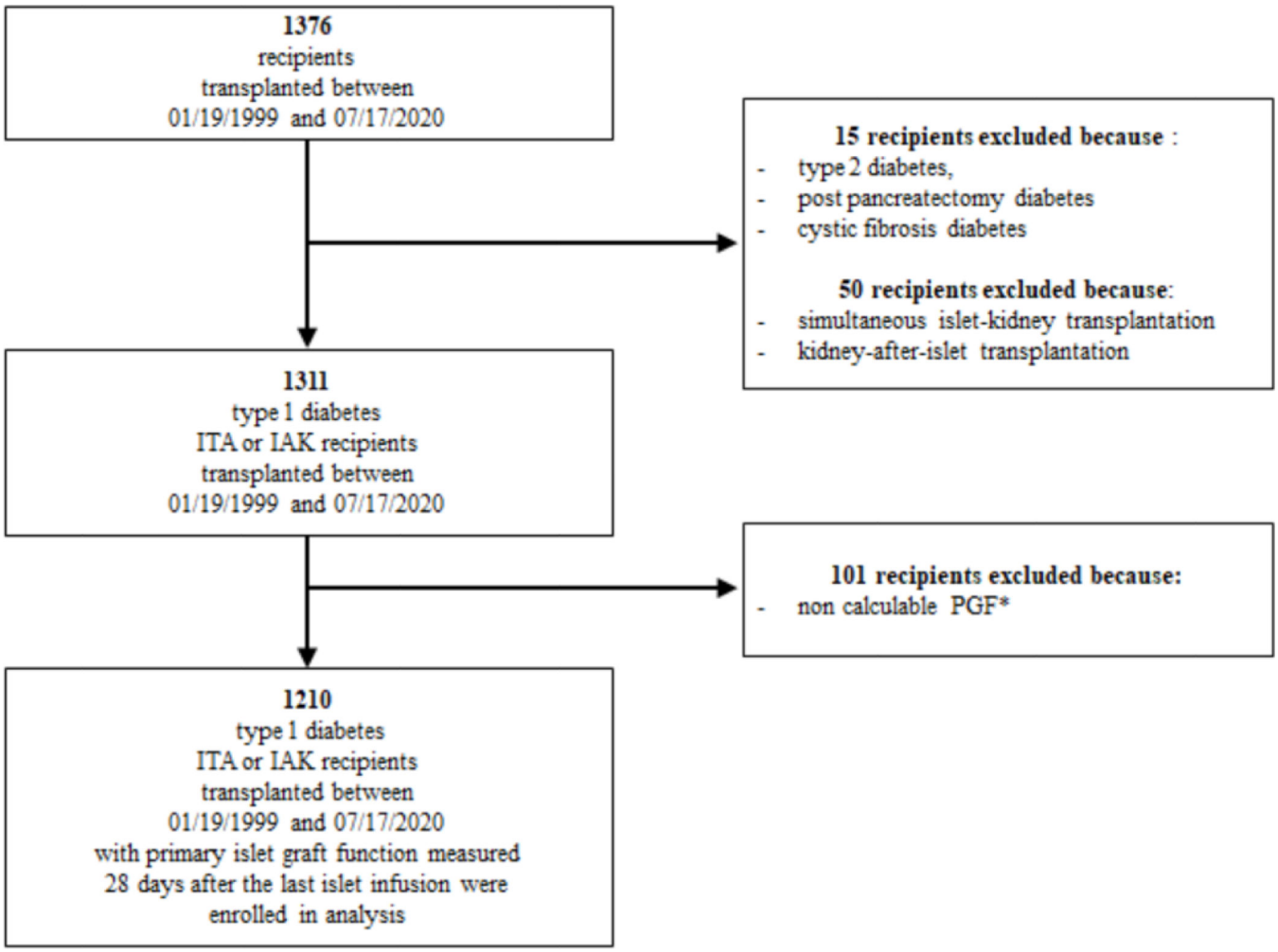


Figure 1: Flow chart of the 1210 recipients enrolled in the study analysis

* PGF (Beta2-score measured at day 28 after the last islet infusion) was not calculable, even after imputations (all data missing) in 101 patients.

Abbreviations: IAK= Islet-After-Kidney recipient; ITA= Islet Transplantation Alone recipient; PGF=Primary Graft Function.

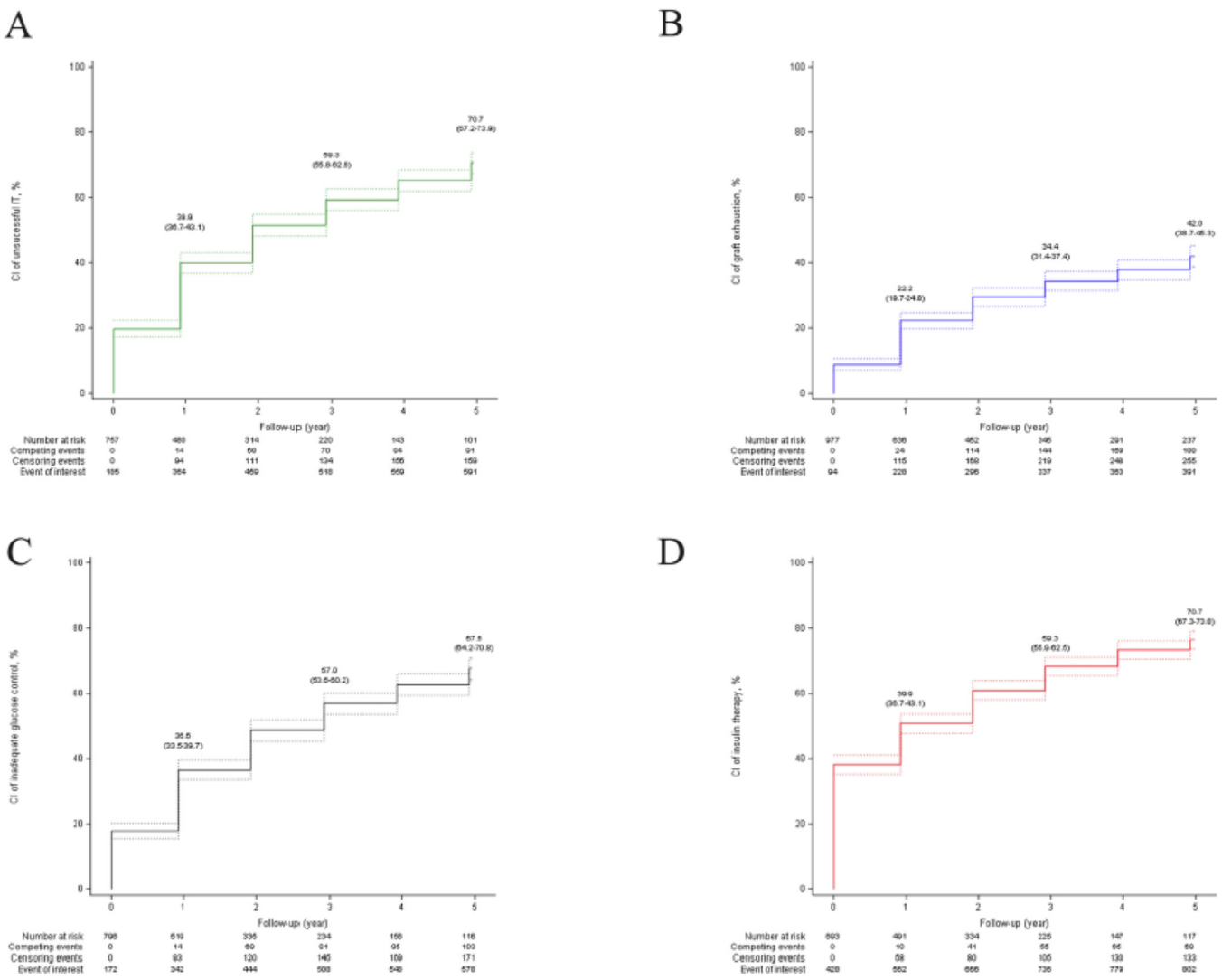


Figure 2: 5-year cumulative incidence of unfavorable outcomes of islet transplantation: unsuccessful IT (Panel 2A), graft exhaustion (Panel 2B), inadequate glucose control (Panel 2C) and exogenous insulin therapy (Panel 2D).

Cumulative incidence curves following the 5 years follow-up are shown as solid lines and 95% confidence intervals as dashed lines for the four unfavorable outcomes: unsuccessful IT (green), graft exhaustion (blue), inadequate glucose control (black), and the need for exogenous insulin therapy (red). Unsuccessful islet transplantation was defined by glycated hemoglobin level greater than or equal to 7.0 % (53 mmol/mol) and/or with at least one episode of severe hypoglycemia since the last visit and/or with serum fasting C-peptide secretion less than 0.2 ng/mL. Graft exhaustion was defined by fasting C-peptide level inferior to 0.3 ng/mL. Inadequate glucose control was defined by glycated hemoglobin greater than or equal to 7.0 % (53 mmol/mol) and/or with at least one episode of severe hypoglycemia since the last visit. The need for exogenous insulin therapy was defined as the administration of exogenous insulin during at least 14 consecutive days.

For each islet transplantation outcomes (unsuccessful IT, graft exhaustion, inadequate glucose control and the need for exogenous insulin therapy), we estimated the cumulative

incidence using the Kalbfleisch and Prentice method, considering the day 28 after the last islet infusion as the date of origin (corresponding time point 0 in the figures), and by treating death and delayed islet re-infusion (defined as an islet infusion performed at least one year after the previous islet infusion) as competing events. To handle missing data in Beta2-score components and pre-specified covariates adjustment, we used multiple imputations using the regression-switching approach (chained equations with m = 60 imputations) using all pre-transplant patients characteristics, transplantation characteristics and Beta2-score components at day 28 after the last islet infusion. No imputations were performed on the 4 study outcomes.

Abbreviations: N.= Number; CI= Cumulative Incidence; IT= Islet Transplantation.

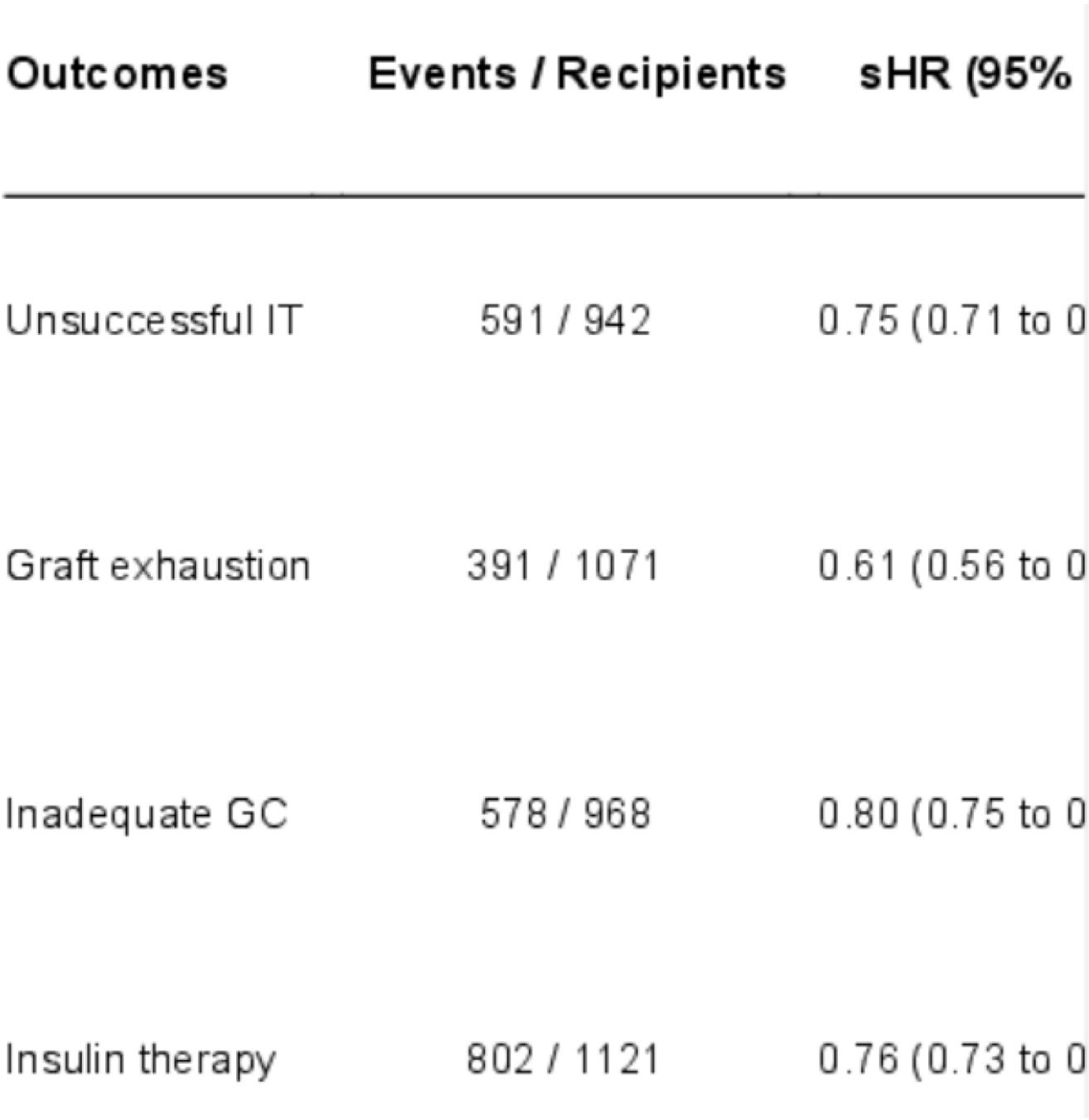


Figure 3: Association of primary graft function and 5-year cumulative incidence of unfavorable islet transplantation outcomes in the whole cohort.

Association of PGF (defined by the Beta2-score at day 28 after the last islet infusion) with cumulative incidence of the four unfavorable islet transplantation outcomes in the whole population: unsuccessful IT (green), graft exhaustion (blue), inadequate glucose control (black), and the need for exogenous insulin therapy (red) are represented with Forest plot. These associations between PGF and islet transplantation unfavorable outcomes were explored using Fine and Gray regression models before and after adjustment on prespecified

covariates suspected or known to impact islet transplantation outcomes and available in the database.

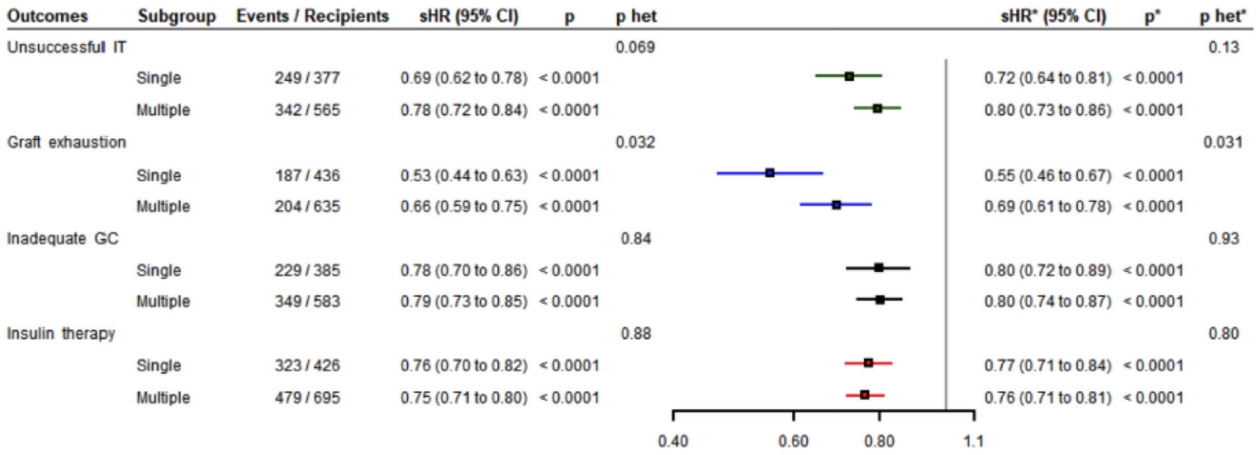
SubHazard ratio (sHR) were calculated for 5 units increase of primary graft function. sHR, 95%CI, and p-values were calculated after handling missing values by multiple imputations using the regression-switching approach (chained equations with m = 60 imputations) using all pre-transplant patients characteristics, transplantation characteristics and Beta2-score components at day 28 after the last islet infusion. sHR and 95% CI are represented in a logarithmic scale.

sHR were adjusted* on baseline (before islet transplantation) recipient age, sex, baseline body mass index, diabetes duration before transplantation, daily exogenous insulin needs at baseline, baseline fasting C-peptide, number of islet infusions, total islet mass transplanted per kg of bodyweight, total cell volume transplanted, type of recipient (ITA or IAK), and the use of specific immunosuppression agents (interleukin 2 receptor antagonist, TNF alpha antagonist, T-cell depleting agent, calcineurin inhibitor and m-TOR inhibitor).

Abbreviations: IT= Islet Transplantation; sHR= subhazard Ratio; 95% CI= 95% Confidence Interval; Inadequate

GC= Inadequate Glucose Control

A



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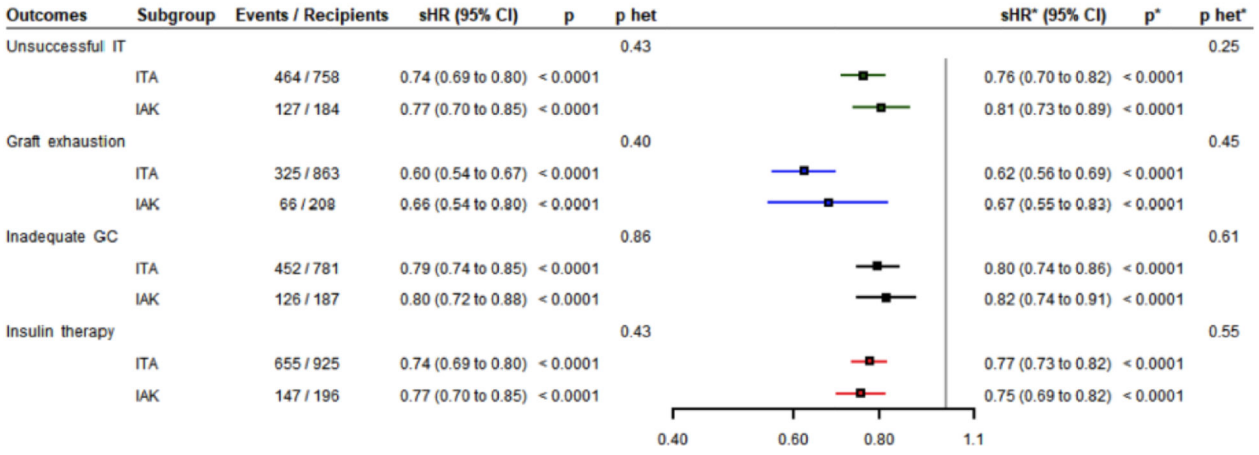

Figure 4: Association of primary graft function and 5-year cumulative incidence of unfavorable islet transplantation outcomes, sensitivity analyses in recipients with single vs. multiple islet infusions transplantation (Panel 4A), and in recipients with ITA vs. IAK recipients (Panel 4B).

Association of PGF (defined by the Beta2-score at day 28 after the last islet infusion) with cumulative incidence of the four unfavorable islet transplantation outcomes in single vs. multiple islet infusions and in ITA and IAK recipients subgroups: unsuccessful IT (green), graft exhaustion (blue), inadequate glucose control (black), and the need for exogenous insulin therapy (red) are represented with Forest plot. These associations between PGF and islet transplantation unfavorable outcomes were explored using Fine and Gray regression models before and after adjustment on prespecified covariates suspected or known to impact islet transplantation outcomes and available in the database.

SubHazard ratio (sHR) were calculated for 5 units increase of primary graft function. sHR, 95%CI, and p-values were calculated after handling missing values by multiple imputations using the regression-switching approach (chained equations with m = 60 imputations) using all pre-transplant patients characteristics, transplantation characteristics and Beta2-score

components at day 28 after the last islet infusion. sHR and 95% CI are represented in a logarithmic scale.

sHR were adjusted* on baseline (before islet transplantation) recipient age, sex, baseline body mass index, diabetes duration before transplantation, daily exogenous insulin needs at baseline, baseline fasting C-peptide, number of islet infusions, total islet mass transplanted per kg of bodyweight, total cell volume transplanted, type of recipient, and the use of specific immunosuppression agents (interleukin 2 receptor antagonist, TNF alpha antagonist, T-cell depleting agent, calcineurin inhibitor and m-TOR inhibitor).

Abbreviations: IT= Islet Transplantation; sHR= subhazard Ratio; 95% CI= 95% Confidence Interval; Inadequate GC= Inadequate Glucose Control; p het=p-value for heterogeneity; ITA -= Islet Transplantation Alone; IAK=Islet-After-Kidney

Table 1:

Pre-transplant patient characteristics and transplantation characteristics in the 1210 recipients of the cohort

	Missing values, n (%)	Values
Pre-transplant patient characteristics		
Sex	14 (1.2%)	
Female, n (%)		712 (59.5%)
Male, n (%)		484 (40.5%)
Age, years	13 (1.1%)	47 ±10
Race, n (%)	326 (26.9%)	
White		865 (97.9%)
Black		9 (1.0%)
Asian		3 (0.3%)
Other		7 (0.8%)
ABO blood type, n (%)	133 (11.0%)	
O group		444 (41.2%)
A group		470 (43.6%)
Other groups		163 (15.2%)
Body Mass Index, kg/m^2	400 (33.1%)	23.7 ±3.0
Duration of type 1 diabetes, years	206 (17.0%)	30.4 ±11.2
Daily exogenous insulin needs, IU/kg/day	272 (22.5%)	0.6 ±0.2
HbA1c, %	205 (16.9%)	7.8 (7.0–8.8)
Fasting blood glucose, mg/dL	391 (32.3%)	157 (103–222)
Fasting C-peptide, ng/mL	334 (27.6%)	0.00 (0.00–0.09)
History of severe hypoglycemia episodes	186 (15.4%)	731(7.4%)
Transplantation characteristics		
ITA / IAK recipients, n (%)	13 (1.1%)	986 (82.4%) / 211 (17.6%)
Duration on islet transplantation waiting list, months	372 (30.7%)	7.1 (2.6–16.1)
Number of pancreas isolated per recipient	298 (24.6%)	2.0 (1.0–3.0)
Number of infusions per recipient	0	2.0 (1.0–2.0)
Recipients with a single islet infusion, n (%)	0	452 (37.4%)
Recipients with multiple islet infusions, n (%)	0	758 (62.6%)
Recipients with 2; 3; ≥ 4 infusions, n (%)	0	632 (83%); 119 (16%); 7 (1%)
Time between first and last infusion, months	3 (0.4%)	4.1 (2.2–6.5)
Recipients with all infusions in ≤ 3; 3 to ≤ 6; 6 to ≤ 12 months, n (%)	3 (0.4%)	279 (37%); 249 (33%); 227 (30%)
Time between first and second infusion, months	3 (0.4%)	3.5 (1.7–6.0)
Time between second and third infusion, months	0	2.1 (1.1–4.0)
Time between third and last infusion, months	0	0.5 (0.1–1.3)
Total islet mass transplanted, per 10^3 IEQ	286 (23.6%)	728 (485–935)
Total islet mass transplanted, per 10^3 IEQ/kg of bodyweight	362 (29.9%)	10.8 (7.4–13.5)
in single islet infusion recipients		6.8 (5.4–9.2)
in multiple islet infusion recipients		12.4 (10.5–15.2)

	Missing values, n (%)	Values
Pre-transplant patient characteristics		
Patients transplanted with < 5; 5 to <10; 10 to <15; ≥15, 10^3 IEQ/kg of bodyweight, n (%)	362 (29.9%)	65 (8%); 291 (34%); 341 (40%); 151 (18%)
Total islet cell volume transplanted, mL	398 (32.9%)	5.0 (3.0–7.5)
Immunosuppression regimens received, n (%)	62 (5.1%)	
T-cell depleting agent		525 (45.7%)
Interleukin 2 receptor antagonist		519 (45.2%)
TNF alpha antagonist therapy		425 (37.0%)
Calcineurin inhibitor		1096 (95.5%)
m-TOR inhibitor		619 (53.9%)

Available data in the 1210 recipients of the CITR cohort are reported as number (percentage), mean ± standard deviation or median (25th-75th percentile) as appropriate. Number (percentage) of recipients with missing values are presented.

Abbreviations: IEQ=islet-equivalent (one islet-equivalent corresponds to the tissue volume of one spherical islet with a diameter of 150 μm); HbA1c= glycated hemoglobin; ITA= Islet Transplant Alone recipient; IAK= Islet-After-Kidney recipient; TNF= Tumor Necrosis Factor; m-TOR= mammalian target of rapamycin

Table 2:

Predicted 2-year and 5-year incidences of patients with islet transplantation unfavorable outcomes according to PGF values measured 28 days after the last islet infusion with the Beta2-score.

	Unsuccessful IT		Graft exhaustion		Inadequate GC		Insulin therapy	
PGF	2-year	5-year	2-year	5-year	2-year	5-year	2-year	5-year
0	77	94	69	89	68	88	83	95
5	67	88	51	74	60	82	74	90
10	56	80	36	56	52	75	64	83
15	47	70	24	40	44	67	54	74
20	38	59	15	27	37	58	45	64
25	30	49	10	17	31	50	36	54
30	24	40	6	11	26	43	29	45
35	18	32	4	7	21	36	23	37
40	14	25	2	4	17	30	18	29

Values are the predicted probabilities (expressed in %) of cumulative incidence of islet transplantation unfavorable outcomes according to PGF value measures 28 day after the last infusion.

Abbreviations: PGF= Primary Graft Function; Inadequate GC= Inadequate Glucose Control; IT= islet transplantation