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A Multicenter Study: North American Islet Donor Score in Donor Pancreas Selection for Human Islet Isolation for Transplantation

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Abstract

Selection of an optimal donor pancreas is the first key task for successful islet isolation. We conducted a retrospective multicenter study in 11 centers in North America to develop an islet donor scoring system using donor variables. The data set consisting of 1,056 deceased donors was

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Disclosures

The authors of this manuscript have no conflicts of interest to disclose.

used for development of scoring system to predict islet isolation success (defined as post-purification islet yield >400,000 islet equivalents). With an aid of univariate logistic regression analyses, we developed North American Islet Donor Score (NAIDS) ranging 0 through 100 points. The c-index in the development cohort was 0.73 [95% confidence interval 0.70 - 0.76]. The success rate increased proportionally as NAIDS increased, from 6.8% success in NAIDS < 50 points to 53.7% success in NAIDS ≥ 80 points. We further validated NAIDS using a separate set of data consisting of 179 islet isolations. Comparable outcome of NAIDS was observed in the validation cohort. The NAIDS may be a useful tool for donor pancreas selection in the clinical practice. Apart from its utility in clinical decision-making, the NAIDS may also be used in research setting as a standardized measurement of pancreas quality.

Keywords

islet isolation; islet transplantation; organ donor; pancreas

Introduction

Allogeneic islet transplantation (AIT), a beta cell replacement therapy, is used in a highly select group of patients with type 1 diabetes. These patients suffer from recurrent severe hypoglycemic episodes and extensive glycemic liability. AIT is a minimally invasive therapeutic procedure compared to whole pancreas transplantation restoring physiological glycemic control without severe complications. Since the Edmonton Protocol was published in 2000 (31), AIT has been applied in many institutions worldwide. Improved islet processing technique as well as clinical immunosuppressive regimens implemented in following years allowed for enhanced short and long term metabolic control, comparable to results after whole pancreas transplantation (1,2). The routine transition of islets collected and transplanted from 2 to 4 donors down to 1 donor per recipient has become a critical for advancement of the field from logistic, medical and financial point of view (32). It would allow also limiting recipient's exposure to multiple donor HLA-antigens and immunologic sensitization. Based on current experience minimal islet mass required for the initial transplantation, with expected substantial metabolic effect, has been set for 5,000 islet equivalent (IEQ) per kilogram of recipient's body weight (32). Therefore, islet processing centers have focused on improving isolation results in order to consistently obtain higher islet yields. Islet isolation results depend on two major factors-characteristics of the donor/pancreas and islet processing technique. Currently after more than a decade of technical efforts, islets processing techniques appear to have reached a mature and stable stage. The selection of an optimal donor pancreas remains an initial key task prior to the islet isolation. It is inarguable that despite the best islet processing technique, islet isolation fails when poor quality donor/pancreas is chosen.

There are two categories of donor variables, which are correlated with islet isolation outcomes: variables predicting pancreas weight and variables related to pancreas quality. Pancreas weight predictors are donor age, gender, body surface area (BSA), body mass index (BMI), body weight (BW), and body height (4,9-19,21,24,27,30,34-36). The pancreas quality predictors are following: cold ischemia time (CIT), donor age, blood chemistry

indicating function of pancreas, liver and kidney, medical history, cause of death, duration of hospital stay, vasopressor usage and organ procurement team (3,6,8,11,17,18,21,22,26,27,34,36). To standardize the pancreatic donors using a combined donor variables approach, O'Gorman et al published the first study with an islet donor score resulting from variables of 326 donors between 1999 and 2004 in a single center (26). As islet mass required for transplant remains >5,000 IEQ per kg of recipient BW, in our analysis we defined successful islet isolation as those with a post-purification islet yield greater than 400,000 IEQ, which is the highest cut off value among those defined in the previous studies (9,11,12,22). With this rigorous definition, transplant can be accomplished in most of the patients, all those with weight ≤80 kg. Herein we report our findings from a multi-center study, where donor variables were weighted to produce a new donor scoring system, which can be used as a routine objective tool for pancreas selection prior to islet isolation in the clinical practice.

Materials and Methods

Study cohort

We conducted a retrospective multicenter study of 1,235 islet preparations obtained from deceased donors at 11 centers in North America (University of Alberta in Canada, Baylor University in Dallas, University of California San Francisco, University of Chicago, University of Illinois at Chicago, Massachusetts General Hospital, University of Miami, University of Minnesota, Allegheny Health Network Pittsburgh, PA, University of Pennsylvania, University of Wisconsin). The data set consisted of 1,056 islet isolation procedures performed between March 2007 and December 2013 was used for the development of a scoring system using donor variables to predict islet isolation outcome (development cohort). For validation purposes, a separate cohort of islet preparations was analyzed. This validation cohort was derived from 179 consecutive islet isolations performed between February 2013 and January 2015 at the largest volume center among 11 centers. This study protocol was reviewed and approved by the Institutional Review Board (IRB) of Division of Biological Sciences, University of Chicago and was identified as non-human subjects research determination under the Federal Regulations. All donor data were entered in REDCap Project in the University of Chicago website before analysis. Based on communication with IRB at the University of Chicago (IRB12-2187), the study did not require review by IRB of other 10 centers.

Outcome

Our outcome measure of interest was post-purification islet yield as expressed in IEQ. Islet yield was determined by manual count of dithizone-stained samples, converting the different islet sizes into IEQ (15). Successful islet isolation was defined as post-purification islet yield greater than 400,000 IEQ. Within the development cohort, there were 29 cases with missing post-purification IEQ data but post-culture IEQ data presented [mean± standard deviation (SD) culture time was 47.8±10.4 hours]. For those cases, we used post-culture IEQ as the measure of islet isolation outcome. Cases other than successful islet isolation were labelled as failed islet isolation.

Donor variables

Candidate predictor variables used in the analyses were age, gender, BW, height, BMI, BSA calculated with the Mosteller formula (23), CIT, cause of death, length of hospitalization, vasopressor requirement, procurement team, medical history, and blood test values including maximum and minimum glucose, peak levels of amylase, lipase, aspartate transaminase (AST), alanine transaminase (ALT), blood urea nitrogen (BUN), creatinine, sodium, and hemoglobin A1c (HbA1c). Cause of death was categorized into cerebrovascular accident, anoxia (including donation after cardiac death), head trauma with abdominal injury, head trauma without abdominal injury, and others. Procurement team was recorded as own or distant dependent on whether or not the team was related to islet isolation center. Length of hospitalization was stratified into 4 categories: < 2, 2-4, 5-7, and > 7 days. Vasopressor requirement was stratified into 5 categories based on the number of different agent types used in donor: none, single, double, triple, and more than three agents. Regarding medical history, the following information was collected: alcohol abuse, hypertension, and cardiac arrest.

Development and validation of scoring system

Using the development cohort, we conducted univariate logistic regression analyses to identify donor variables that predict islet isolation success. We then created donor scoring systems (points from 0 to 100) consisting mainly of several donor variables influencing outcome. We plotted receiver operating characteristic (ROC) curve for each scoring system. We calculated area under the curve (AUC) (also referred as c-index) to assess the ability of scoring system to predict successful islet isolation. We identified a scoring system having the highest AUC and named it North American Islet Donor Score (NAIDS). Finally we tested the validity of NAIDS on the validation cohort. Based on communication with IRB at University of Chicago (IRB12-2187), the study did not require review by the IRB.

Statistical analysis

Continuous variables are presented as mean ± SD. Categorical variables are shown as the percentage of the sample. A p-value < 0.05 was considered significant. Univariate logistic regression analyses and unpaired t-test were conducted using SPSS version 19 (SPSS Inc., Chicago, IL). The comparison of two uncorrelated ROC was based on a form of a Z statistic that uses the difference in the area under the two curves and the standard error of each AUC.

Results

Donor characteristics

The donor characteristics of 1,056 islet isolations are shown in Table 1. The mean age of donors was 45.8 years, and ranged from 5 to 77 years. The proportion of male donors was 55.5%. Cerebrovascular accident accounted for the most frequent causes of death. The proportion of donors receiving zero, single, double, and triple vasopressor therapy during their hospital stay was 14.4, 38.0, 26.3, and 14.5%, respectively. Mean CIT was 9.4 hours, ranging from 0.67 to 23.8 hours. The majority of donors stayed in the hospital for less than 5 days. Mean amylase and lipase peak levels were 136 and 78 U/L, respectively. Mean

maximum and minimum blood glucose levels were 235 and 119 mg/dL, respectively. Mean HbA1c was 5.6% but data were available in only 552 cases (52.3%).

Univariate logistic regression analyses

Of the 1,056 analysed cases, 286 (27.0%) were successful islet isolations. Univariate logistic regression analyses revealed that the following donor variables were significantly associated with successful islet isolation: greater height, greater BW, greater BMI, larger BSA, male gender, shorter CIT, lower peak blood glucose, lower sodium level, pancreas procured by own team, less number of different vasopressor types, and the presence of cardiac arrest (Table 2).

Donor score

Initially we employed a previously published method (33) to create a simplified scoring system based on multivariate logistic regression model and estimated the score weights. However, we obtained an unsatisfactory scoring system with a ROC-AUC of 0.681, which has a poor discriminative ability. Therefore, we empirically created 87 different donor scoring systems with an aid of the results of univariate logistic regression analyses. Among 87 systems, a donor scoring system with the highest AUC value, hereafter referred as the NAIDS, is presented in Table 3. The NAIDS is comprised of three main influential donor variables (BSA, number of different vasopressor types, and BMI) and two supplemental composite factors (unfavorable and favorable factors). Some of variables in the NAIDS were not statistically significant in the univariate analyses, but by including non-significant variables as a composite factor, the NAIDS obtained an AUC of 0.730 [95% confidence interval 0.697 - 0.763] (Figure 1). A brief explanation as to how we created the NAIDS should be provided. High amylase and lipase levels are both generally considered undesirable, but only amylase level was included into the NAIDS because we found that including lipase level did not gain extra increase in an AUC. We found that CIT of pancreas procured by own team was significantly shorter than that of distant team procured pancreas (5.9±2.6 vs 10.5±3.8 hours, $P<0.001$, t-test). Thus procurement team was highly associated with CIT. However excluding one of those factors from the NAIDS resulted in a lesser AUC value, leading us to include them both-CIT and procurement team into the NAIDS. Finally the threshold of biochemical test such as AST, ALT, BUN, and amylase was manually determined to obtain the highest possible AUC.

Success rate based on NAIDS

We grouped the NAIDS into 5 strata to allow the application of NAIDS stratification for comparisons of outcomes. The success rate increased proportionally as the NAIDS increased, from 6.8% (14/206) success in NAIDS < 50 points to 53.7% (102/190) success in NAIDS ≥ 80 points (Figure 2).

Validation of NAIDS

For validation of the NAIDS, we plotted ROC curve using the validation cohort data (n=179). The ROC-AUC was 0.713 [95% confidence interval 0.637 - 0.788] (Figure 3), which was not significantly different ($P=0.67$) from that obtained from the development

cohort. Furthermore, a similar proportional increase in a success rate was observed as the NAIDS increased in the validation cohort (Figure 2).

Discussion

The NAIDS is a comprehensive scoring system. It consists of donor variables that predict pancreas weight and quality out of a total 100 points. A higher NAIDS corresponds to a higher success rate with post-purification IEQ yielding over 400,000.

The NAIDS has three variables for pancreas weight estimation (i.e. BSA, BMI, and BW). BSA is given a maximum of 25 points, followed by BMI with 10 points. BW is allocated into the unfavorable and favorable factors. BMI as a measure for pancreas weight estimation has been used for many years in the islet field. However, it is not a completely accurate indicator. Although the BSA and BMI are both calculated from the body weight and height, the calculation formulas are different. Kin et al reported BW and BSA were more strongly correlated with pancreas weight (14). The NAIDS stresses more on pancreas weight estimation using combined variables of BSA, BMI and BW.

The NAIDS sets 65 points in the estimation of pancreas quality. The human pancreas is a more vulnerable abdominal organ comparing to others like liver and kidney. Islets as a tiny endocrine organ represent approximately 1 to 2% of total pancreatic tissue and are surrounded by acinar cells containing protease. Most researchers believe that early activation of intracellular zymogen in the process of acute pancreatitis leads to a trypsin cascade that subsequently causes auto-digestion of acinar cells (7). It is clear that a pancreas with chronic pancreatitis is not a suitable donor organ. However, even in stable but brain dead conditions, donor may suffer from impaired vascular autoregulation and decreased tissue perfusion pressure that subsequently cause decline in tissue perfusion and hypoxemia of the pancreas. It can evoke cellular damage and further result in autodigestion of pancreatic tissue. A study (16) in a rat model showed that exocrine tissue injury occurred with dynamic amylase release during pancreas preservation at 4°C. Furthermore islet injury was found to correlate with amylase release and led to a reduced number and viability of isolated islets. Loganathan et al (20) reported that human isolated islet loss after culture was significantly higher in impure relative to pure preparations. Furthermore lower islet purity was associated with many potentially drawbacks including increased protease activity and decreased insulin levels in culture supernatants with reduced beta-cell insulin granules and enhanced insulin degradation by proteases. Finally islet transplantations in mice showed delayed islet graft function when acinar cells were transplanted adjacent to the islets under the kidney capsule. The above studies indicated that autodigested acinar cells in pancreatic injury might also contribute to the low yield and impaired function in isolated islets. We believe that even if the impaired tissue perfusion and present hypoxemia are corrected before procurement, the autodigested islets are less likely to recover before islet isolation.

No usage of vasopressor usage is awarded a maximum of 15 points in the NAIDS. When a dose of one type of vasopressor exceeds a certain level, the use of additional vasopressor is generally required. The need for concomitant use of vasopressors indicates hemodynamic instability leading to the poor blood microcirculation in the donor pancreas and progressing

pancreatic injury. Therefore, the use of more different types of vasopressor is likely to result in lower islet yield.

If there is no unfavorable factor, 35 points is given. Although islets obtained from younger donors are functionally superior to islets from older donors, the technical challenges in obtaining purified high quality islets are not overcome with lower donor age, especially below 20 years old. Conversely, donors > 70 years old are not considered an ideal donor since insulin secretory capacities deteriorate with increasing age (10). Longer CIT significantly decreases post-purification islet recovery. Many investigators found that the CIT shorter than 2 hours had negative impact on islet yield, although the mechanism is not clear (personal communications). Abnormally high values of ALT, AST, BUN, and amylase can be a result of multiple organ failure, where the pancreas is often involved. HbA1c > 6.5% suggests the donor suffered from diabetes. It has been reported that islets isolated from type 2 diabetic donor pancreas had impairment of islet function and lower islet yield (28).

Favorable factors are given a maximum of 15 points. Own procurement team often provides higher quality organ recovery, which includes more efficient flush with preservation solution and cooling of donor pancreas after cross clamp, especially during multiorgan procurement. When blood sodium level is elevated (>160 mEq/L) for certain period of time, cell dehydration within the donor body occurs and therefore islets also become compromised. Even when the high blood sodium levels are corrected, the pancreatic injury may not be reversible. A study by Qi et al (29) reported hypernatremia is associated with reduced islet recovery in the post culture and diminished efficacy of islets when transplanted into diabetic mice. Donor high blood glucose levels indicate islet dysfunction and it is recognized as a negative factor in the scoring system.

Previous studies identified cardiac arrest as a negative variable, which was predicting a low islet yield (3,18). In contrast, our univariate logistic regression analysis resulted in a positive impact of the presence of cardiac arrest. It has been reported that the substantially increased risk of cardiovascular diseases was associated in patients with being overweight or obese (5). Therefore, possible confounding relationship between the presence of cardiac arrest and high BMI might explain our unexpected finding. However, that was not the case. There was no statistical difference in BMI between cardiac arrest and no arrest cases (29.4±6.5 vs 28.8±6.5 kg/m^2, P=0.25, t-test). Our observation is most likely a statistical artefact created by the skewed distribution of frequency in cardiac arrest among the centers. In fact, the highest volume center (contributing 383 cases in the development cohort) exhibited 64% of cardiac arrest cases (122/190), and the center had the highest number of successful isolation cases (n=131). This skewed distribution was also probably due to difference in interpretation of cardiac arrest across centers and may represent a reporting error. We recognize this as a limitation of our study.

Three additional limitations potentially existed in this multicenter study. First, we set the post-purification IEQ > 400,000 as the target measurement for this study. After an optimal donor pancreas is received, there are several steps of the islet isolation procedure that may additionally affect the post-purification yield. Deviations or mistakes at any step can compromise the islet yield. We did not analyze the technical deviations in the isolation steps

in involved centers. It is reasonable to assume that the rate of post-purification IEQ over 400,000 is higher in cases where the technical deviations or mistakes did not occur. The second, every islet center uses the same principle to count islets and to calculate the IEQ. However, technical deviations involved in IEQ counts may exist in each islet team. Deviations may occur during sample preparation, sampling methods and the counting of islets. An over-counted IEQ may increase the successful islet isolation rate in the low NAIDS group. Vice versa, an under-counted IEQ may decrease the successful islet isolation rate in the high NAIDS group. When all technical steps are under better-standardized control, we would expect a better correlation between NAIDS and post-purification IEQ > 400,000. The third, any deficiency of ice-cold protection of donor pancreas during procurement or transportation may result in warm ischemia injury. This kind of injury cannot be accounted for by the NAIDS since the injury is usually undetected or not recorded. In such cases, even donor pancreas with high NAIDS is highly susceptible to produce poor islet yield.

This study established the NAIDS based on data from 1,235 islet isolation cases of the multicenter international database. The NAIDS shows the most important donor variables with quantitative scores. The application of NAIDS will provide useful reference for the selection of ideal pancreata for successful islet isolation and transplantation. In current analysis, we did not analyse predictive value of NAIDS, as we did not want to set cut off for organ utilization. NAIDS provides information of the chance of successful islet isolation based on score and allows each individual center to set own cut off depending on risk willing to take, logistic situation, funding available, clinical scenario of the recipient. For example, centers with very limited funding or starting the program, may choose focus of the best donors/organs, for example NAIDS >80, waiting longer for availability of such optimal organs, but optimizing own islet processing system in the best organ scenario, gaining the experience. With time, they may choose to be more aggressive, lowering the threshold for NAIDS, processing more organs and transplanting more patients in shorter period of time. Apart from its utility in clinical decision-making, the NAIDS may also be used in a research setting as a standardized measurement of pancreas quality.

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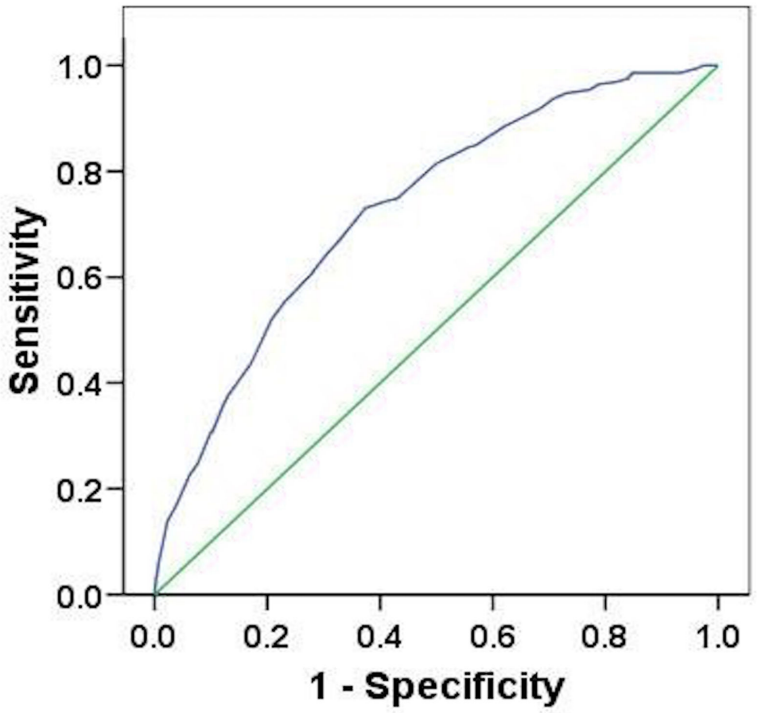

Figure 1.

Receiver-operating characteristics (ROC) curve of the NAIDS in the development cohort. Blue line indicates ROC curve and green line indicates diagonal reference. Area under the curve was 0.730 (95% confidence interval, 0.697-0.763).

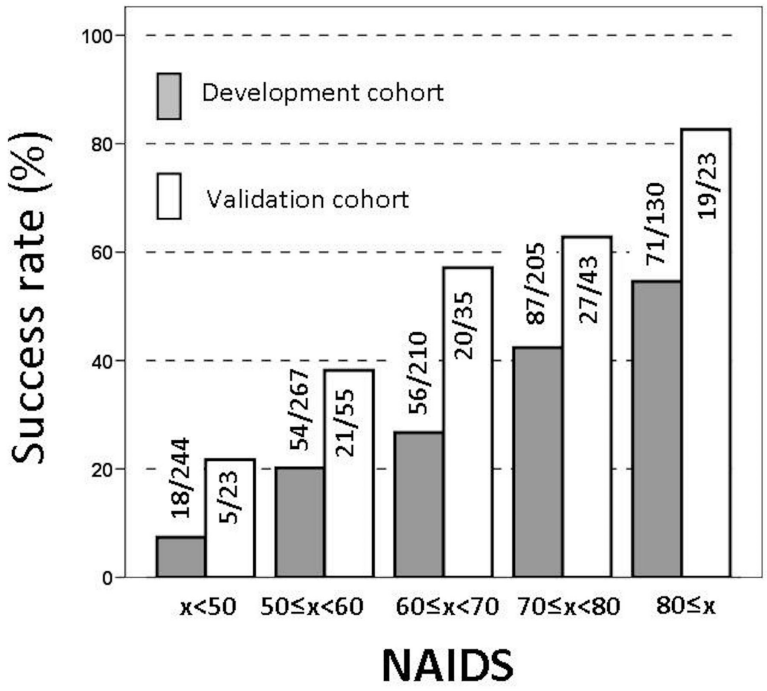

Figure 2.

Successful islet isolation rate by the NAIDS for both development and validation cohorts. The success rate increased proportionally as the NAIDS increased in both development and validation cohorts.

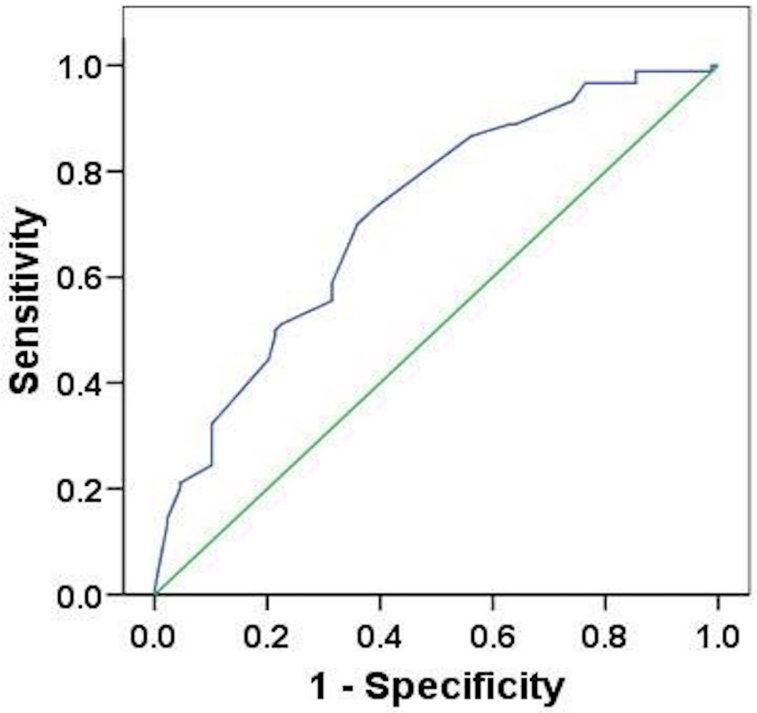

Figure 3.

Receiver-operating characteristics (ROC) curve of the NAIDS in the validation cohort. Blue line indicates ROC curve and green line indicates diagonal reference. Area under the curve was 0.713 (95% confidence interval, 0.637-0.788).

Table 1

Donor Characteristics in the Development Cohort: Continuous Variables

Variables	*N*	Mean ± SD	Range
Age (year)	1,056	45.8 ± 13.2	5–77
Height (cm)	1,055	171.8 ± 10.6	125–210
Body weight (kg)	1,055	85.6 ± 21.3	25–200
Body mass index (kg/m^2)	1,055	28.9 ± 6.5	13.3–66.6
Body surface area (m^2)	1,055	2.01 ± 0.28	0.97–3.21
Cold ischemia time (h)	1,056	9.4 ± 4.1	0.67–23.9
Amylase (U/L)	955	136 ± 206	5–1,953
Lipase (U/L)	906	78 ± 125	3–1,186
AST (U/L)	1,002	101 ± 229	5–4,092
ALT (U/L)	1,007	81 ± 181	4–3,268
HbA1c (%)	552	5.6 ± 0.7	3.5–14.6
Peak glucose (mg/dl)	804	235 ± 83	79–982
Lowest glucose (mg/dl)	804	119 ± 36	15–311
BUN (mg/dl)	1,039	19 ± 12	2–105
Creatinine (mg/dl)	1,043	1.6 ± 2.5	0.3–75
Na (mEq/L)	1,025	150.7 ± 9.8	125–189

Table 2

Donor Characteristics in the Development Cohort: Categorical Variables

Variables	N (%)
Gender	
Male	586 (55.5)
Female	470 (44.5)
Cause of death	
Cerebrovascular accident	590 (55.9)
Anoxia	136 (12.9)
Head trauma with abdominal injury	23 (2.2)
Head trauma without abdominal injury	304 (28.8)
Others	3 (0.3)
Procurement team	
Own	247 (23.4)
Distant	808 (76.6)
Missing	1 (0.1)
Hospital stay	
<2 days	247 (23.4)
2–4 days	604 (57.2)
5–7 days	133 (12.6)
>7 days	64 (6.1)
Missing	8 (0.8)
Vasopressor use	
None	152 (14.4)
Single	401 (38.0)
Double	278 (26.3)
Triple	153 (14.5)
More than three	47 (4.5)
Missing	25 (2.4)
Medical history *	
Alcohol abuse	152 (14.4)
Hypertension	362 (34.3)
Cardiac arrest	190 (18.0)
Absence of above three	479 (45.4)

* 115 cases have multiple events.

Table 3

Univariate Logistic Regression Analyses for Prediction of Successful Islet Isolation

		95% Confident Interval		
	Odds Ratio	**Lower**	**Upper**	***p* Value**
Age (year)	1.002	0.991	1.012	0.767
Height (cm)	1.022	1.009	1.036	0.001
Body weight (kg)	1.026	1.019	1.033	<0.0001
Body mass index (kg/m^2)	1.078	1.055	1.102	<0.0001
Body surface area (m^2)	7.423	4.424	12.457	<0.0001
Cold ischemia time (h)	0.938	0.906	0.972	0.0004
Amylase (U/L)	0.999	0.999	1.000	0.205
Lipase (U/L)	0.999	0.998	1.001	0.398
AST (U/L)	1.000	0.999	1.000	0.277
ALT (U/L)	1.000	0.999	1.001	0.921
HbA1c (%)	0.914	0.698	1.197	0.514
Peak glucose (mg/dl)	0.998	0.996	0.999	0.026
Lowest glucose (mg/dl)	1.003	0.999	1.008	0.097
BUN (mg/dl)	1.011	0.999	1.022	0.066
Creatinine (mg/dl)	1.014	0.965	1.065	0.584
Na (mEq/L)	0.983	0.969	0.997	0.020
Male gender	1.433	1.086	1.892	0.011
Own team procurement	1.705	1.256	2.315	<0.001
Less vasopressor use	1.328	1.158	1.523	<0.0001
Longer hospital stay	1.100	0.926	1.308	0.278
Cause of death				
Cerebrovascular accident	1.107	0.841	1.456	0.468
Anoxia	1.051	0.703	1.570	0.809
Head trauma with abdominal injury	0.949	0.370	2.432	0.913
Head trauma without abdominal injury	0.881	0.650	1.194	0.415
Medical history				
Alcohol abuse	1.201	0.824	1.749	0.341
Hypertension	0.999	0.751	1.330	0.995
Cardiac arrest	1.430	1.020	2.006	0.038

Table 4

North American Islet Donor Score

Body surface area (m^2)	
X < 1.54	0
1.54 ≤ X < 1.82	5
1.82 ≤ X < 2	10
2 ≤ X < 2.18	20
2.18 ≤ X	25
Number of vasopressor types used	
More than 2	0
Double	3
Single	10
None	15
Body mass index (kg/m^2)	
X < 20.1	0
20.1 ≤ X < 28.1	2
28.1 ≤ X < 32.5	7
32.5 ≤ X < 52.0	10
52.0 ≤ X	0
Unfavorable factors *	
At least one	0
None	35
Favorable factors †	
None	0
One	2
Two	7
More than two	15

* Unfavorable factors: age (years) <20, >75; CIT (h) ≤2, >17; body weight (kg) <55; HbA1c (%) >6.5; ALT (U/L) >1,070; AST (U/L) >580; BUN (mg/dl) ≥80; amylase (U/L) >1,500.

† Favorable factors: body weight (kg) >120; own team procurement; 130 < Na (mEq/L) < 160; peak glucose (mg/dl) <410.