




**BRIEF COMMUNICATION****BETA-2 score is an early predictor of graft decline and loss of insulin independence after pancreatic islet allotransplantation**

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This study aimed to evaluate whether the BETA-2 score is a reliable early predictor of graft decline and loss of insulin independence after islet allotransplantation. Islet transplant procedures were stratified into 3 groups according to clinical outcome: long-term insulin independence without islet graft decline (group 1, N = 9), initial insulin independence with subsequent islet graft decline and loss of insulin independence (group 2, N = 13), and no insulin independence (group 3, N = 13). BETA-2 was calculated on day 75 and multiple times afterwards for up to 145 months posttransplantation. A BETA-2 score cut-off of 17.4 on day 75 posttransplantation was discerned between group 1 and groups 2 and 3 (area under the receiver operating characteristic 0.769,  $P = .005$ ) with a sensitivity and negative predictive value of 100%. Additionally, BETA-2  $\geq 17.4$  at any timepoint during follow-up reflected islet function required for long-term insulin independence. While BETA-2 did not decline below 17.4 for each of the 9 cases from group 1, the score decreased below 17.4 for all transplants from group 2 with subsequent loss of insulin independence. The reduction of BETA-2 below 17.4 predicted 9 (1.5-21) months in advance subsequent islet graft decline and loss of insulin independence ( $P = .03$ ). This finding has important implications for posttransplant monitoring and patient care.

**KEYWORDS**

clinical research/practice, diabetes: type 1, islet transplantation, islets of Langerhans, quality of care/care delivery

**1 | INTRODUCTION**

Islet transplantation (ITx) is offered to patients with brittle type 1 diabetes mellitus (T1DM) with the goal of restoring normoglycemia and preventing severe hypoglycemic episodes while reducing or even eliminating the need for exogenous insulin support. Human islet graft

recovery and complete engraftment into the liver parenchyma after intraportal infusion may take several weeks and is considered accomplished by 2-3 months after transplantation.<sup>1-3</sup> Since posttransplant proliferation of human islets has never been documented, the ultimate long-term outcome of ITx depends on the persistence and function of the engrafted islet mass after intraportal infusion. Insufficient

**Abbreviations:** AUROC, area under the receiver operating characteristic; BETA-2, BETA-2 score; HbA1c, hemoglobin A1c; IEQ, islet equivalent units; ITx, islet allotransplantation; ROC, receiver operating characteristic.

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islet engraftment is clinically apparent when the insulin dose cannot be further decreased without compromising blood glucose control. However, even when a state of insulin independence is reached, its durability remains uncertain.<sup>4</sup> Optimal engraftment of the islet mass results in stable long-term graft function, whereas suboptimal engraftment leads to islet exhaustion and deterioration, ultimately resulting in the clinical need for the resumption of insulin support.

Initial islet graft decline is only evident in subtle subclinical changes in blood glucose control that could previously only be detected using metabolic stimulation tests, which carry substantial logistical burdens.<sup>5</sup> The recently developed BETA-2 score can measure islet function with the precision of stimulation tests but is logistically more convenient and based on information from a single blood sample (fasting blood glucose, C-peptide, and hemoglobin A1c [HbA1c]).<sup>6,7</sup>

The aim of the current study was to verify the clinical utility of the BETA-2 score. We used both retrospective analysis and prospective observation to assess whether BETA-2 can reliably predict upcoming graft failure before the need for insulin reintroduction, which would enable potentially graft-saving therapeutic intervention.

## 2 | METHODS

### 2.1 | Study design and cohort

We analyzed data from islet transplantation procedures performed at the University of Chicago between 2005 and 2015 for patients with long-standing and brittle T1DM. Participants provided written informed consent and the study was approved by the University of Chicago Institutional Review Board. Our islet transplantation technique and particular strategy for the discontinuation or re-initiation of exogenous insulin after transplantation was previously discussed.<sup>8,9</sup> ITx represented the first, second, or third distinct islet infusion for each patient, and islet graft function as well as outcomes were assessed after each individual procedure with a follow-up of 3 months or longer. Since the quantity of infused islet mass (islet equivalent units; IEQ), immunosuppressive protocols, anti-inflammatory regimens, and history of prior transplantation varied between patients, we did not assess islet graft function in relation to these factors but instead focused our analysis on the correlation between the BETA-2 score and islet graft function and long-term outcome.

Islet transplants were stratified into 3 groups according to clinical outcome: long-term and stable insulin independence without islet graft decline (group 1), insulin independence with subsequent islet graft decline over time and loss of insulin independence (group 2), and no insulin independence (group 3). We adopted previously established criteria for insulin independence.<sup>10</sup> Optimal islet graft function was defined based on the IGLs Classification.<sup>11</sup>

### 2.2 | Metabolic assays

Serum glucose and C-peptide were measured at the University of Chicago Medicine laboratory or locally. Body weight and insulin use

(average daily insulin dose over the previous 7 days divided by body weight in kilograms) were extracted from medical records and patient diaries.

### 2.3 | BETA-2 score

BETA-2 score was calculated from the fasting blood glucose (mmol/L), C-peptide (nmol/L), HbA1c (%), and insulin dose (U/kg per day) as described by Forbes et al<sup>6</sup>

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

### 2.4 | Statistical analyses

Descriptive statistics included median, range, and percentages. Receiver operating characteristic (ROC) curves were drawn to discriminate between group 1 and groups 2 and 3. Youden's index was calculated (specificity + sensitivity-1) and used to select the optimal cut-off value. Kaplan-Meier curves were created for the duration of insulin-independent survival according to a determined value (cut-off) that discriminates between transplants with and without declining islet function. ROC curves were also created for glucose, c-peptide, and HbA1c levels to determine sensitivity and specificity values needed to differentiate between BETA-2 above and below the previously established cut-off value. ROC (AUROC) curves were compared between groups to determine which measures detected the outcome with sufficient discrimination. Correlation between BETA-2 and fasting c-peptide-to-glucose ratio was calculated using Spearman-rank correlation coefficient for each transplant in group 1. Throughout our study,  $P < .05$  was considered statistically significant. Statistical analyses were performed using Statistica software (Dell, Aliso Viejo, CA).

## 3 | RESULTS

Thirty-five islet transplant procedures were performed in 16 patients (8 female and 8 male). Four patients received a single islet transplant, 5 patients received 2 transplants, and 7 patients received 3. The median IEQ and IEQ/kg per transplant were 445 833 (256 095-719 998) and 6 187 (3 398-11 077), respectively. Among the 35 islet transplant procedures assessed in our study, 9 (26%) resulted in stable long-term insulin independence without islet graft decline during follow-up (group 1). In contrast, 13/35 (37%) transplants led to initial insulin independence followed by islet graft decline and the clinical need for reinitiation of exogenous insulin (group 2). For the remaining 13/35 (37%) transplants, insulin independence was never achieved (group 3). The median follow-up was 54 months (17-145).

### 3.1 | Detection of stable vs deteriorating islet graft function on day 75 post-ITx

All transplants in group 1 resulted in optimal islet engraftment and function on day 75, allowing for stable long-term insulin independence without subsequent islet graft decline. A BETA-2 score of 17.4 on day 75 post-islet infusion was found to be a reliable cut-off value for differentiating group 1 from groups 2 and 3 (AUROC 0.769,  $P = .005$ ). The negative predictive value was 100%, indicating that none of the transplants with a BETA-2 score of  $<17.4$  on day 75 resulted in stable long-term insulin independence. The sensitivity was also 100%, indicating that all transplants with such a successful outcome had a BETA-2 of 17.4 or higher on day 75. The positive predictive value was 47%, reflecting the fact that only 47% of transplants with a BETA-2 of 17.4 or higher on day 75 presented with stable insulin independence over the long term, with many recipients likely losing insulin independence due to subsequent islet loss via rejection, recurrent autoimmunity, drug toxicity, or other factors. The observed reduction in specificity to 61.5% could also be attributed to these factors. As a result, a BETA-2 score of  $<17.4$  on day 75 identified 61.5% of all transplants that did not result in long-standing insulin independence.

Group 2 represented transplants that enabled insulin independence on day 75 but not throughout the follow-up period. This raised the possibility that a subset of patients might have had less-than-optimal beta cell mass engraftment that could allow for only temporary insulin independence followed by gradual islet graft deterioration from exhaustion. Among others, 3 transplants (23%) from group 2 resulted in insulin independence on day 75, but with BETA-2 scores already below the threshold of 17.4 (12.7, 15, and 16.9) that further declined until the loss of insulin independence 3, 4, and 5 months posttransplantation, respectively. In addition, all transplants from group 3 had a BETA-2 score of  $<17.4$  on day 75 and never achieved insulin independence.

### 3.2 | Detection of stable vs deteriorating islet graft function after day 75 post-ITx and prediction of return to exogenous insulin therapy

Furthermore, we tested whether a BETA-2 cut-off value of  $\geq 17.4$  reflected stable and optimal islet function not only on day 75 but also at later timepoints during subsequent follow-up. We analyzed BETA-2 trends starting from day 75 after each transplant separately for groups 1 and 2 and collected a total of 199 BETA-2 values (median 19 values per transplant [range 10-51] over a median of 4.5 years [range 1.5-12]). Figure 1A,B displays BETA-2 trends over time for recipients from group 1, whose BETA-2 fluctuated between 17.4 and 38. Figure 1A represents data from 4 patients who received only 1 islet infusion and Figure 1B from 5 other individuals after a final (second or third) islet infusion. For all 9 patients, the BETA-2 score did not drop below 17.4 during the follow-up period, indicating that a BETA-2 of 17.4 and above represented stable and optimal islet function not only on day 75 but also at any timepoint afterwards in our cohort.

A similar analysis of BETA-2 trends over time was completed for patients from group 2 who experienced a known decline of islet graft function and loss of insulin independence at some point during follow-up. One hundred six BETA-2 scores (range 10.4-27.4) were collected prior to the reintroduction of exogenous insulin support. The median for the lowest BETA-2 score after each transplant, immediately before the reintroduction of exogenous insulin, was 13.6 (10.4-16.4). All BETA-2 scores were  $<17.4$ , our calculated cut-off for optimal islet function. Altogether, a reduction of BETA-2  $<17.4$  predicted islet graft decline and the loss of insulin independence. Of note, once BETA-2 dropped below 17.4, it did not increase above that cut-off for all cases in group 2. The range of BETA-2 and the corresponding graft function for each individual transplant from group 2 is presented in Figure 2. Kaplan-Meier analysis demonstrated that a decline of BETA-2  $<17.4$  appeared a median of 9 months (range 1.5-24) prior to the loss of insulin independence for all 13 patients in group 2 ( $P = .008$ ) (Figure 3).

### 3.3 | Prospective validation of findings

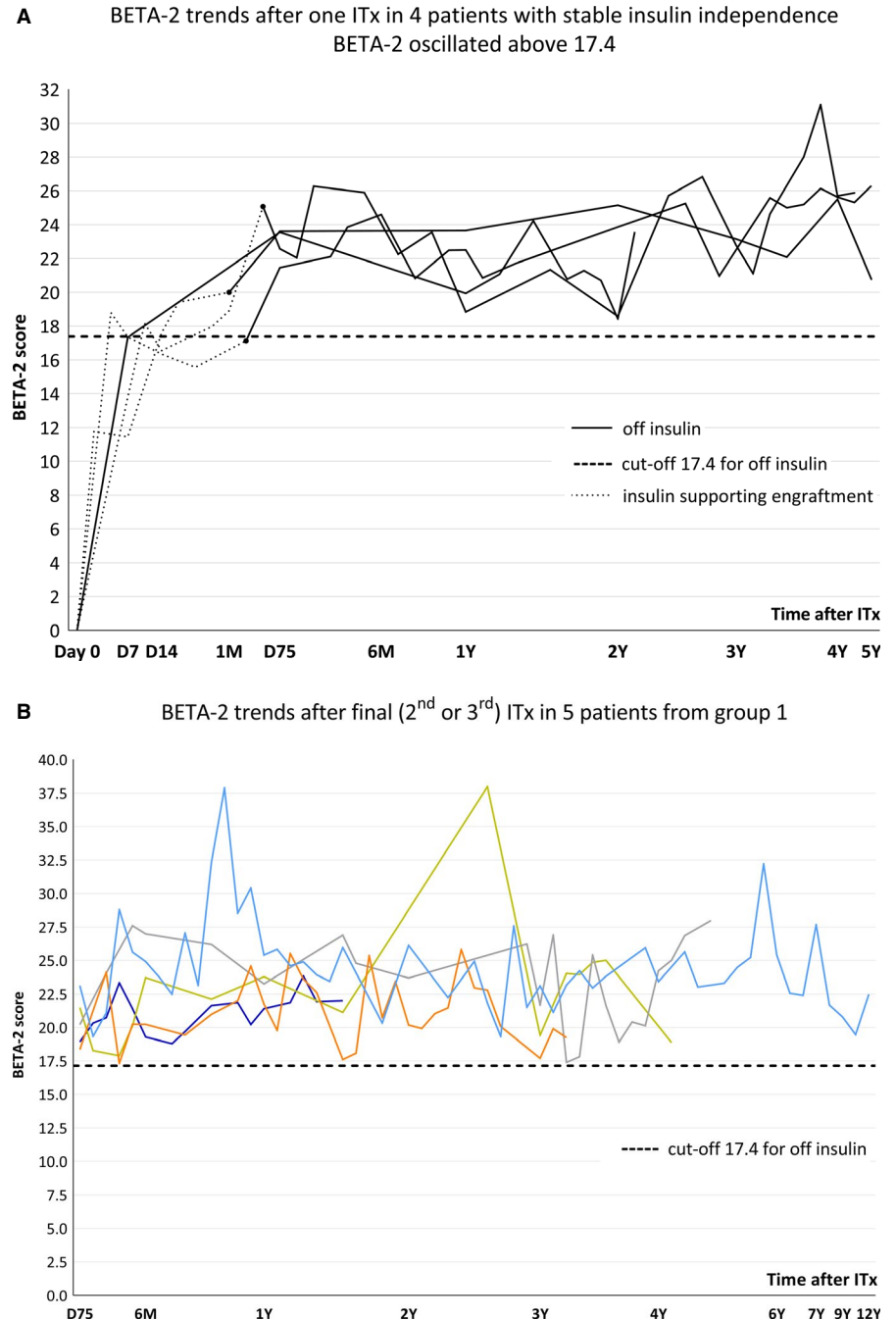
Following the initial analysis of BETA-2 trajectories, we verified our findings prospectively. We collected BETA-2 scores from the same cohort of transplants over 18 subsequent months. One patient from group 1 withdrew consent from participation in our study and was not included in the prospective analysis. Seven of the remaining 8 recipients maintained insulin independence with a BETA-2 score of at least 17.4 at each of the 69 assessed timepoints. For the remaining case (12.5%), the BETA-2 score dropped to 16.95 and gradually declined to 11.13 at 18 months, when insulin support needed to be reinitiated. This observation confirmed previous conclusions that stable optimal islet graft function is represented by a BETA-2 score of at least 17.4 and that a drop of the BETA-2 score  $<17.4$  predicted the further decline of islet graft function and the subsequent need for insulin support.

We also prospectively collected data on 13 transplants from group 2 requiring insulin support. In 1 case, a patient who needed minimal insulin supplementation decreased his carbohydrate intake and was able to stop insulin again for limited durations (1-2 months) 5 different times. However, each time insulin support was ceased, his BETA-2 score remained below 17.4. Nine months later, the patient became fully insulin-dependent with a BETA-2  $<10$ , requiring much higher doses of exogenous insulin. The remaining 12 (92%) transplant recipients were neither able to stop insulin support nor achieve a BETA-2 score of at least 17.4 without subsequent ITx, which was in accordance with findings from our retrospective analysis.

### 3.4 | Correlation between BETA-2 score and insulin resistance measured by fasting c-peptide to glucose ratio after islet transplants with long-term insulin independence (in group 1)

Since we noticed a fluctuation of the BETA-2 score  $>17.4$  over time despite stable islet graft function and insulin independence for

**FIGURE 1** A, Trends of BETA-2 score in 4 patients from group 1 with persistent insulin independence after only 1 islet transplant. Stable and optimal islet graft function is represented by BETA-2 values oscillating  $>17.4$  after postinfusion day 75. Insulin supplementation was implemented to support islet engraftment and was ceased by day 75. B, BETA-2 score trends after the final (second or third) islet infusion in 5 patients from group 1 with stable optimal islet function and long-term insulin independence. Optimal islet graft function was represented by BETA-2 values  $>17.4$  at any timepoint during follow-up. ITx, islet transplantation

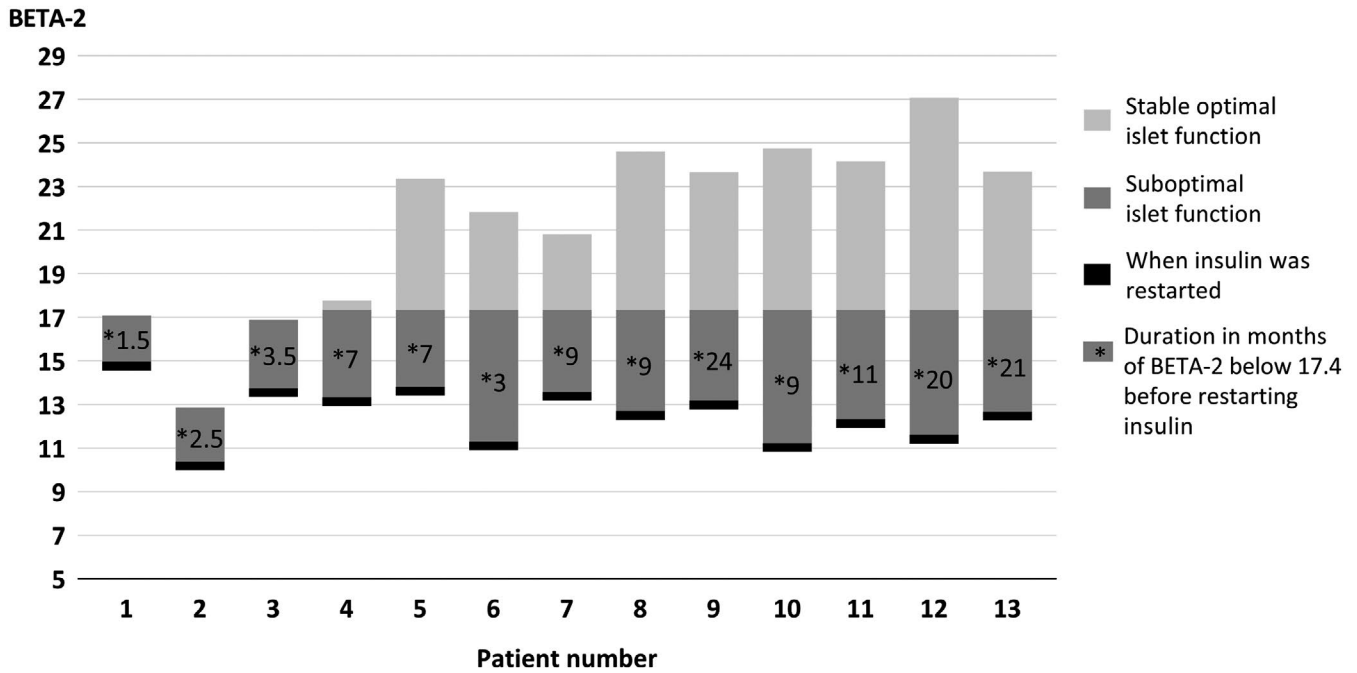


transplants in group 1, we decided to test whether BETA-2 oscillations result from variability of insulin resistance. We analyzed the correlation between BETA-2 and fasting c-peptide to glucose ratio, one of the known indices assessing insulin resistance.<sup>12</sup> There was a very strong positive correlation between BETA-2 and c-peptide-to-glucose ratio during the follow-up period for transplants in group 1 (median  $r = .804$  [0.57-0.895]) ( $P < .006$ ). The correlation after each individual transplant is presented in Table 1. Thus, the fluctuation of BETA-2 over 17.4 in patients with optimal islet graft function and long-term insulin independence was related to changes in insulin resistance.

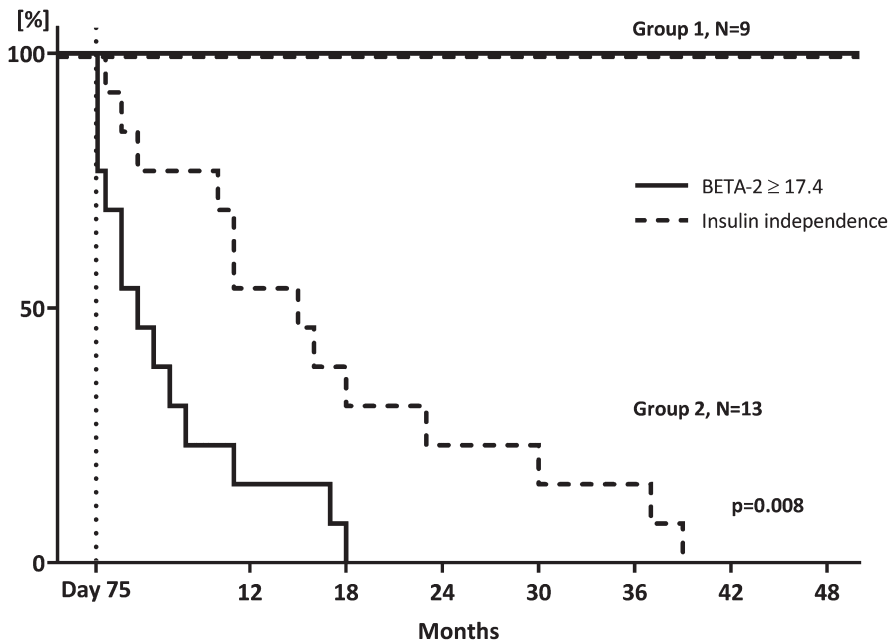
### 3.5 | Utility of a single fasting glucose, fasting c-peptide, or A1c level for the discrimination between stable and deteriorating islet function

Finally, we evaluated whether separate single values of fasting glucose, c-peptide, or HbA1c can differentiate between stable optimal islet function and islet function predicting graft decline and the loss of insulin independence at any time during follow-up. We compared values of fasting blood glucose at timepoints of BETA-2  $\geq 17.4$  to those collected at timepoints corresponding to BETA-2  $< 17.4$  but prior to the reinitiation of insulin support

### Ranges of BETA-2 depending on islet function for each transplant in group 2



**FIGURE 2** Ranges of BETA-2 score after each transplant from group 2 depending on islet function until the reintroduction of insulin support. Light gray part of the bar represents the BETA-2 score range over the cut-off 17.4 established for stable optimal islet function. Dark gray part of the bar represents the range of BETA-2 between the cut-off of 17.4 and the reintroduction of insulin support. Black horizontal line in each bar represents BETA-2 value when insulin was restarted. Numbers in the dark gray part (\*) represent the duration in months between the drop of BETA-2 <17.4 and the reintroduction of insulin support for each transplant (number of months BETA-2 drop <17.4 preceded loss of insulin independence)



**FIGURE 3** Kaplan-Meier analysis of BETA-2 ≥ 17.4 and insulin independence after postinfusion day 75 for patients from groups 1 and 2. Insulin independence and the incidence of BETA-2 scores ≥17.4 remained 100% for group 1 during follow-up, whereas both values declined for group 2. The decline of BETA-2 <17.4 preceded the loss of insulin independence for all 13 patients in group 2 (Kaplan-Meier P = .008). The median lag between the decline of BETA-2 <17.4 and the loss of insulin independence was 9 mo (range 1.5-24)

(12.7-17.40). The same comparison was performed for fasting c-peptide and HbA1c (Figure 4). For most measurements, discrimination between BETA-2 above and below 17.4 based on a single

value of fasting glucose, c-peptide, or A1c was not possible because we found a wide overlap of fasting glucose, c-peptide, and HbA1c values between stable optimal islet function and islet

**TABLE 1** Correlation between BETA-2 score and insulin resistance measured by fasting c-peptide-to-fasting-glucose ratio after islet transplantations, which resulted in long-term insulin independence (group 1)

Group 1 (N = 9) Transplant number	R	P
1	.782589	.000001
2	.793014	.000001
3	.867692	.000001
4	.570158	.004504
5	.889687	.000001
6	.741259	.005801
7	.804348	.000002
8	.825159	.000001
9	.895105	.000084

function predicting graft decline. Only extreme values allowed for an accurate distinction. Nevertheless, further analysis showed a discriminative value for each of these standard measures based on ROC AUC analysis (Table 2). Fasting plasma glucose distinguished stable optimal islet function from islet function predicting graft decline significantly better than A1c and fasting c-peptide ( $P < .001$ ) and could be utilized as an estimate measure if the BETA-2 score is not available.

## 4 | DISCUSSION

Monitoring graft function after islet transplantation is considerably more challenging than after transplantation of the pancreas or another solid organ. A criterion standard assessment through a graft biopsy is not possible, and no verified simple diagnostic tool or clinically reliable marker is currently available to diagnose early ongoing islet allograft loss.<sup>5</sup> Islet graft function and glucose control can remain unaffected despite islet damage and declining beta cell mass, further complicating analyses. As much as 80%-90% of native islet mass can be lost before glucose intolerance is detected.<sup>13</sup>

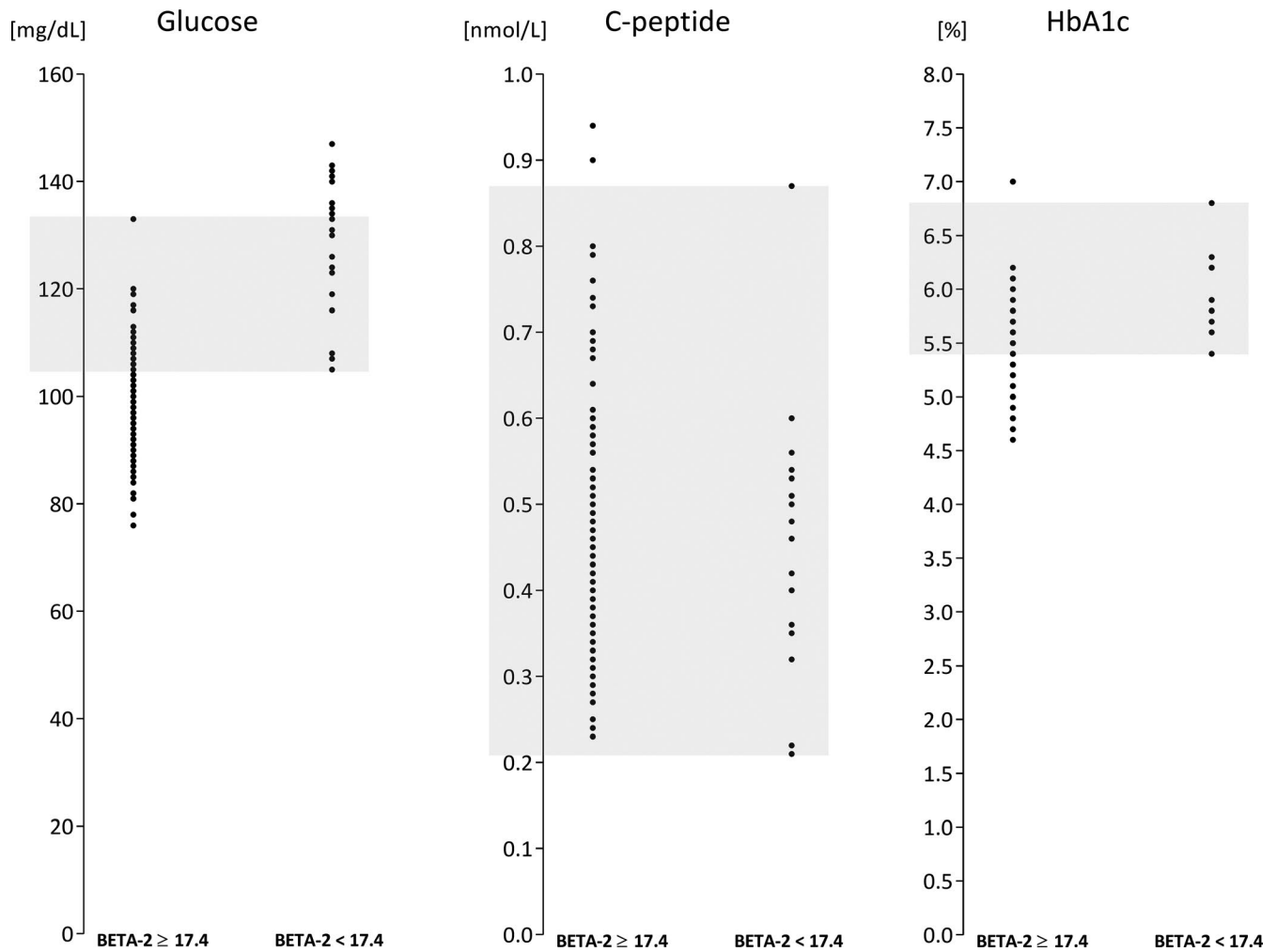
The original validation of the BETA-2 score by Forbes et al presented the ability of BETA-2 to detect insulin independence and glucose intolerance at the time of measurement. BETA-2 showed >88% specificity and sensitivity in detecting insulin independence with a cut-off of 15, whereas a BETA-2 cut-off of 20 had >82% sensitivity and specificity in detecting glucose intolerance.<sup>6</sup> Our subsequent external BETA-2 validation presented very similar results.<sup>14</sup> We also used BETA-2 to measure islet graft function on day 75 and found that it can also predict insulin independence at 1 year posttransplantation (AUC = 0.942 [0.869-1]) ( $P = .001$ ).<sup>15</sup> In the current analysis, we found additional benefit of BETA-2 measurement for the monitoring of islet graft function and the prediction of islet graft outcome. We identified that a BETA-2 score cut-off of 17.4 has 100% sensitivity and negative predictive value for the prediction of long-term insulin independence. BETA-2 measurement in insulin-independent

patients allows for (1) the detection of subclinical deterioration of islet graft function, which could result in the subsequent need to resume insulin support (if BETA-2 is <17.4) and for (2) the detection of islet graft function, which enables long-term insulin independence in the absence of additional islet insults (BETA-2 > 17.4). Our results are complementary with previous findings, highlighting the utility of BETA-2 for multiple assessments and the prediction of islet graft function.

We also showed that a BETA-2 score of  $\geq 17.4$  reflected optimal and stable islet graft function at the time of measurement. This finding has critical practical value, reassuring a patient and their physician of graft integrity and functionality during follow-up. Interestingly, in our analysis we found that insulin-independent patients with optimal islet graft function experienced BETA-2 score fluctuations >17.4. Since we found a very strong positive correlation between BETA-2 and the fasting c-peptide-to-glucose ratio, we concluded that these BETA-2 fluctuations were related to variability in insulin resistance over time. This could be related to metabolic changes in a patient secondary to weight loss or gain, infection, or changes in medication dosage. The observation that BETA-2 oscillations reflect changes in fasting blood glucose, c-peptide, and HbA1c in transplant recipients despite stable islet graft function highlights the notion that the individual monitoring of fasting values could be misleading and confusing, supporting the utility of BETA-2 assessment.

Additionally, we found that the drop of BETA-2 <17.4 was always followed by a gradual islet graft decline months before the clinically detectable deterioration of blood glucose control and loss of insulin independence. In such cases, BETA-2 never returned >17.4 unless the patient received a subsequent islet transplant. Therefore, we concluded that a decrease of BETA-2 below 17.4 reflected diminished function of the suboptimal islet mass as a result of either insufficient engraftment or ongoing graft loss. Our findings may enable a prompt implementation of diagnostic and therapeutic tools, extending the time frame to facilitate the prevention of further graft decline, importantly before extensive islet loss results in the need for exogenous insulin support.

Although we did not observe donor-specific HLA antibodies or a specific pattern of autoantibodies in our cohort, cellular rejection or recurrent T1DM might still have been a cause of islet graft decline. Therefore, given the limitations of available methods for the detection of cellular allo- or autoimmune reactivity in the context of islet transplantation, a critical need exists for the development of new diagnostic tools capable of detecting and defining mechanisms of islet loss with high levels of accuracy in advance of clinical manifestation. The BETA-2 score could help to guide the optimal timing of their application prior to extensive islet loss. In addition, the BETA-2 score may also serve as a valid end-point in clinical trials to measure improvements in beta-cell function following novel therapeutic approaches. In the event of insufficient islet engraftment, decisions regarding subsequent transplants can also be made more quickly and based on objective measurements.



**FIGURE 4** Fasting glucose, c-peptide, and HbA1c values at timepoints when patients were still off insulin for BETA-2 ≥ 17.4 and for BETA-2 < 17.4. There was considerable overlap of fasting glucose, c-peptide, and HbA1c values between the 2 groups marked as a gray zone. There are also extreme values (outside the gray zone), which allowed for apparent BETA-2 range discrimination. HbA1c, hemoglobin A1c

We found the BETA-2 score to be such a reliable, replicable, precise, and convenient tool for monitoring islet graft function that, following this study, we abandoned the use of stimulation tests for this purpose in our clinical practice. The simplicity of monitoring islet graft function with BETA-2 allows for a higher frequency of testing and the earlier detection of islet dysfunction in contrast to seldomly performed and cumbersome mixed meal tolerance tests. Local physicians can also easily implement BETA-2, supporting the treatment of patients living far from diabetes centers. Of note, we showed that fasting blood glucose better correlated with BETA-2 than single fasting c-peptide or HbA1c level.

In the event of inadequate data for the calculation of the BETA-2 score, the increase of fasting blood glucose >113 mg/mL could be used to approximate islet graft function and predict the loss of insulin independence (BETA-2 < 17.4).

Limitations of our study include a small cohort and a single-center trial with a specific strategy for patient management, islet isolation, and transplantation. Nevertheless, we found our results to be of remarkable clinical importance. To the best of our knowledge, this is the first study evaluating the clinical utility of the BETA-2 score for the long-term monitoring of patients undergoing islet transplantation. These data offer valuable insights regarding the interpretation

	Cut-off	AUROC 95% CI	P value	Sensitivity (%)	Specificity (%)
Fasting plasma glucose	>113	0.953 (0.921-0.986)	.0001	81	96
HbA1c	>5.9	0.760 (0.692-0.829)	.0001	75	71
Fasting c-peptide	<0.44	0.696 (0.620-0.772)	.0001	75	59

**TABLE 2** AUROC of glucose, c-peptide, and HbA1c levels that differentiates between BETA-2 ≥ 17.4 and BETA-2 < 17.4

AUROC, areas under the receiver operating characteristic; CI, confidence interval; HbA1c, hemoglobin A1c.

of BETA-2 and indicate an effective cut-off for the assessment of islet function.

BETA-2 is a simple and objective tool for the assessment of islet engraftment and graft function following transplantation. The score discriminates stable from progressively declining islet function and extends the time frame for diagnostic and therapeutic interventions prior to the loss of the islet graft.

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## DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## REFERENCES

- Eich T, Eriksson O, Lundgren T. Visualization of early engraftment in clinical islet transplantation by positron-emission tomography. *N Engl J Med*. 2007;356(26):2754-2755.
- McCall M, Shapiro AM. Update on islet transplantation. *Cold Spring Harb Perspect Med*. 2012;2(7):a007823.
- Rickels MR, Robertson RP. Pancreatic islet transplantation in humans: recent progress and future directions. *Endocr Rev*. 2019;40(2):631-668.
- Rickels MR, Liu C, Shlansky-Goldberg RD, et al. Improvement in  $\beta$ -cell secretory capacity after human islet transplantation according to the CIT07 protocol. *Diabetes*. 2013;62(8):2890-2897.
- Dy EC, Harlan DM, Rother KI. Assessment of islet function following islet and pancreas transplantation. *Curr Diab Rep*. 2006;6(4):316-322.
- Forbes S, Oram RA, Smith A, et al. Validation of the BETA-2 score: an improved tool to estimate beta cell function after clinical islet transplantation using a single fasting blood sample. *Am J Transplant*. 2016;16:2704-2713.
- Ryan EA, Paty BW, Senior PA, et al. Beta-score: an assessment of beta-cell function after islet transplantation. *Diabetes Care*. 2005;28:343-347.
- Tekin Z, Garfinkel MR, Chon WJ, et al. Outcomes of pancreatic allotransplantation using the Edmonton protocol at the University of Chicago. *Transplant Direct*. 2016;13:2.
- Vantghem M-C, Raverdy V, Balavoine A-S, et al. Continuous glucose monitoring after islet transplantation in type 1 diabetes: an excellent graft function ( $\beta$ -score greater than 7) is required to abrogate hyperglycemia, whereas a minimal function is necessary to suppress severe hypoglycemia ( $\beta$ -score greater than 3). *J Clin Endocrinol Metab*. 2012;97:E2078-E2083.
- Bellin MD, Kandaswamy R, Parkey J, et al. Prolonged insulin independence after allotransplants in recipients with type 1 diabetes. *Am J Transplant*. 2008;8:2463-2470.
- Rickels MR, Stock PG, de Koning E, et al. Defining outcomes for  $\beta$ -cell replacement therapy in the treatment of diabetes: a consensus report on the IgIs criteria from the IPITA/EPITA opinion leaders workshop. *Transplantation*. 2018;102(9):1479-1486.
- Ohkura T, Shiochi H, Fujioka Y, et al. 20/(fasting C-peptide  $\times$  fasting plasma glucose) is a simple and effective index of insulin resistance in patients with type 2 diabetes mellitus: a preliminary report. *Cardiovasc Diabetol*. 2013;22:12-21.
- Herold KC, Usmani-Brown S, Ghazi T, et al.  $\beta$  cell death and dysfunction during type 1 diabetes development in at-risk individuals. *J Clin Invest*. 2015;125:1163-1173.
- Gołębiewska J, Solomina J, Kijek MR, et al. External validation of the newly developed BETA-2 scoring system for pancreatic islet graft function assessment. *Transplant Proc*. 2017;49:2340-2346.
- Gołębiewska JE, Solomina J, Thomas C, et al. Comparative evaluation of simple indices using a single fasting blood sample to estimate beta cell function after islet transplantation. *Am J Transplant*. 2018;18:990-997.

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