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BRIEF COMMUNICATION

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Comparative evaluation of simple indices using a single fasting blood sample to estimate beta cell function after islet transplantation

Justyna E. Gołębiewska[1,2] | Julia Solomina[1] | Celeste Thomas[3] | Mark R. Kijek[1] | Piotr J. Bachul[1,4] | Lindsay Basto[1] | Karolina Gołąb[1] | Ling-jia Wang[1] | Natalie Fillman[1] | Martin Tibudan[1] | Kamil Ciepły[1] | Louis Philipson[3] | Alicja Dębska-Ślizień[2] | J. Michael Millis[1] | John Fung[1] | Piotr Witkowski[1]

[1]Department of Surgery, University of Chicago, Chicago, IL

[2]Department of Nephrology, Transplantology and Internal Medicine, Medical University of Gdańsk, Gdańsk, Poland

[3]Department of Medicine, University of Chicago, Chicago, IL

[4]Department of Anatomy, Jagiellonian University Medical College, Krakow, Poland

Correspondence
Piotr Witkowski
Email: pwitkowski@surgery.bsd.uchicago.edu

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Six single fasting blood sample–based indices—Secretory Unit of Islet Transplant Objects (SUITO), Transplant Estimated Function (TEF), Homeostasis Model Assessment (HOMA)2-B%, C-peptide/glucose ratio (CP/G), C-peptide/glucose creatinine ratio (CP/GCr), and BETA-2 score—were compared against commonly used 90-minute mixed meal tolerance test (MMTT) serum glucose and beta score to assess which of them best recognizes the state of acceptable blood glucose control without insulin supplementation after islet allotransplantation (ITx). We also tested whether the indices could identify the success of ITx based on the Igls classification of beta cell graft function. We analyzed values from 47 MMTT tests in 4 patients with up to 140 months follow-up and from 54 MMTT tests in 13 patients with up to 42 months follow-up. SUITO, CP/G, HOMA2-B%, and BETA-2 correlated well with the 90-minute glucose of the MMTT and beta-score (r 0.54-0.76), whereas CP/GCr showed a modest performance (r 0.41-0.52) while TEF showed little correlation. BETA-2 and SUITO were the best identifiers and predictors of the need for insulin support, glucose intolerance, and ITx success ($P < .001$), while HOMA2-B% and TEF were unreliable. Single fasting blood sample SUITO and BETA-2 scores are very practical alternative tools that allow for frequent assessments of graft function.

KEYWORDS

clinical research/practice, islet transplantation, islets of Langerhans, monitoring: physiologic

1 | INTRODUCTION

The assessment of the efficacy of beta cell replacement therapies is compound and reflects the complexity of glucose homeostasis regulation. Appropriate evaluation of beta cell graft function should include the following: average glycemic control, glycemic variability, hypoglycemic awareness, and glucose and C-peptide reaction to a standardized stimulus that triggers an insulin secretory response. However, such comprehensive evaluations are time consuming and logistically challenging for both patients and physicians. An easily accessible graft index is highly desirable to clinically manage islet recipients, so a number of surrogate indices have been developed that

Abbreviations: AIRarg, acute insulin response after the intravenous administration of arginine; AIRglc, acute insulin response after the intravenous administration of glucose; AUROC, area under the receiver operating characteristic; BETA 2, BETA-2 score; CI, confidence interval; CP/G, C-peptide/glucose ratio; CP/GCr, C-peptide/glucose creatinine ratio; DIR, daily insulin requirement; HbA1c, hemoglobin A1c; HOMA2-B%, homeostasis model assessment; IEQ, islet equivalent units; IQR, interquartile range; ITx, islet allotransplantation; LT, long term; MMTT, mixed meal tolerance test; QoL, quality of life; ROC, receiver operating characteristic; SEM, standard error of the mean; ST, short term; SUITO, secretory unit of islet transplant objects; TEF, transplant estimated function.

TABLE 1 Brief characteristics of simple indices using a single fasting blood sample to estimate beta cell function after islet transplantation

Index	Characteristics	Reference
SUITO	SUITO index of 100 reflects 100% pancreatic beta cell function in a healthy person Reflects engrafted islet mass Assesses functional islet mass Correlates well with IVGTT results Correlates with daily insulin dose (a score <10 is associated with increasing insulin dose) Correlates with the severity of hypoglycemic episodes A score >26 detects insulin independence and highly effective prevention of hypoglycemia A score >10 is associated with QoL improvement	1-8
TEF	Estimates the patient's daily amount of secreted insulin, can be normalized to the number of transplanted islets, correlates well with area C-peptide concentration under the curve over 24 h and with the AIRglc, AIRarg	9-10
HOMA2-B%	Assesses functional islet mass The model is calibrated to give normal beta cell function of 100% HOMA2-B% <40 is considered decreased beta cell function in diabetic subjects, correlates well with estimates using continuous infusion glucose model assessment, hyperglycemic clamps, and the acute insulin response from the IVGTT	11
CP/G	Assesses islet graft dysfunction correlates with 90-min Glc after MMTT; AIRglu after IVGTT and with beta score Is superior to the use of C-peptide alone for the detection of graft dysfunction	12
CP/GCr	Assesses islet graft dysfunction Since C-peptide is cleared through the kidney, accounts for renal function Is not superior to the use of C-peptide alone for the detection of graft dysfunction	12
BETA 2	Estimates graft function as a continuous variable within a range 0-42 A score <20 detects glucose intolerance A score ≥15 detects insulin independence	13

AIRglc, acute insulin response after the intravenous administration of glucose; AIRarg, acute insulin response after the intravenous administration of arginine; BETA 2, BETA-2 score; CP/G, C-peptide/glucose ratio; CP/GCr, C-peptide/glucose creatinine ratio; IVGTT, intravenous glucose tolerance test; HOMA2-B%, homeostasis model assessment; MMTT, mixed meal tolerance test; QoL, quality of life; SUITO, secretory unit of islet transplant objects; TEF, transplant estimated function.

utilize data obtained from only a single fasting blood sample and/or patient's history (Table 1).[1–13]

Our objective was to compare the surrogate measures using a single fasting blood sample in order to determine which ones best serve as a simple test for predicting 90-minute glucose after the mixed meal tolerance test (MMTT) and clinical outcomes given by the beta score. We also made an attempt to see whether these could be used to objectively recognize a metabolic state of acceptable blood glucose control without the need for insulin supplementation. Furthermore, we tested the ability of the surrogate indices to identify the success of ITx defined by the Igls classification of beta cell graft function introduced as a consensus statement in the beginning of 2017 during the First IPITA/EPITA Opinion Leaders Workshop in Igls, Austria (Table 2).

2 | PATIENTS AND METHODS

Two cohorts of patients with "brittle" type 1 diabetes mellitus, who participated in clinical studies involving ITx at the University of Chicago between March 2005 and March 2015, were analyzed. Participants provided written informed consent, and the study was approved by the University of Chicago Institutional Review Board. Our strategy for discontinuation or re-initiation of the exogenous insulin after islet transplantation was adopted from an earlier publication.[14]

2.1 | Standard measures for beta cell function based on stimulation studies

2.1.1 | Mixed meal tolerance test (MMTT)

A MMTT was performed after 8 to 12 hours of fasting. Blood samples were collected for the measurement of glucose, C-peptide, and insulin concentrations at baseline and then at 0, 30, 60, 90, and 120 minutes after ingesting 6 mL/kg body weight of BOOST® High-protein (Nestlé; 360 calories, 9 g fat, 49.5 g carbohydrate, 22.5 g protein) with a maximum of 360 mL.

2.1.2 | Beta score

The beta score was calculated from the patient's daily insulin requirements (DIR), hemoglobin A1c (HbA1c), fasting plasma glucose concentration, and stimulated/fasting C-peptide levels according to the method described by Ryan et al.[15]

2.2 | Calculation of the surrogate indices of beta cell function based on fasting blood sample

Secretory unit of islets transplant objects (SUITO) was calculated from the fasting blood glucose (mmol/L) and C-peptide (nmol/L) levels according to the method described by Takita et al.[1-4]

TABLE 2 Igls classification of beta cell graft function introduced as a consensus statement in the beginning of 2017 during the First IPITA/EPITA Opinion Leaders Workshop in Igls, Austria

Functional status	HbA1c (%)	Severe hypo events (SH)	Insulin requirement (U/kg/d)	C-peptide	Success
Optimal	≤6.5	None	No	> Baseline	Yes
Good	<7.0	None	<50% Baseline[c]	> Baseline	Yes
Marginal	≥7.0	< Baseline[a]	≥50% Baseline	> Baseline	No[e]
Failure	Baseline	Baseline[b]	Baseline	Baseline[d]	No

HbA1c, hemoglobin A1c.
[a]If SH was present before beta cell therapy, then continued benefit may require assessment of exposure to severe hypoglycemia (<3 mmol/L), hypoglycemia awareness, and glycemic variability/liability.
[b]If SH was not present before beta cell therapy, then return to baseline measures is used as indication for treatment.
[c]Might include noninsulin antihyperglycemic agents.
[d]Is not reliable in uremic patients with evidence of C-peptide production prior to beta cell therapy.
[e]Clinically, may still decide that benefits of maintaining and monitoring beta cell graft outweigh risks.

$$SUITO = \frac{250 \times fasting\ C-peptide\ [nmol/L]}{fasting\ plasma\ glucose\ [mmol/L] - 3.43}$$

Transplant estimated function (TEF) was calculated from the DIR and HbA1c according to the method previously described.[9,10]

$$TEF = \left[DIRpreTx + \frac{HbA1c\ preTx}{5.43}\right] - \left[DIR + \frac{HbA1c}{5.43}\right]$$

The homeostasis model assessment (HOMA) index of cell function is present in the literature in 2 versions: HOMA1-B% and HOMA2-B%.[10,11] We used the HOMA2-B% method because it can be calculated relying on paired fasting plasma glucose and C-peptide instead of plasma insulin concentrations,[11] calculated with the use of a computer program (HOMA calculator) (www.dtu.ox.ac.uk/index.php?maindoc/homa/index.php).

C-peptide/glucose ratio (CP/G) was calculated from the fasting blood glucose (mg/dL) and C-peptide (ng/mL) levels according to the method described by Faradji et al.[12]

$$CP/G = \frac{\text{fasting C-peptide concentration [ng/mL]}}{\text{fasting plasma glucose concentration [mg/dL]}}$$

C-peptide/glucose creatinine ratio (CP/GCr) was calculated from the fasting blood glucose (mg/dL), C-peptide (ng/mL) and creatinine levels according to the method described by Faradji et al:[12]

$$CP/GCr = \frac{fasting\ C-peptide\ concentration\ [ng/mL]}{fasting\ plasma\ glucose\ concentration\ [mg/dL] \times creatinine\ concentration\ [mg/dL]}$$

BETA-2 score was calculated from the fasting blood glucose (mg/dL), C-peptide (ng/mL), HbA1c (%), and insulin dose (U/kg per day) as described by Forbes et al[13]

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

Igls classification of beta cell graft function was introduced as a consensus statement in the beginning of 2017 during the First IPITA/EPITA Opinion Leaders Workshop in Igls, Austria (Table 2). Optimal or good islet function defined the success of the procedure.

2.3 | Statistical analysis

Data were tested for normality, and Pearson or Spearman rank correlation coefficients were determined, as appropriate. To account for repeated measurements within the same individual, the mixed effects approach described in Hamlett et al[16] was performed. A 2-tailed Student *t* test was used for comparison between groups with continuous variables. Receiver operating characteristic (ROC) curves were made for continuous variables to determine sensitivity and specificity values for predicting insulin independence. ROC curves were constructed for participant's SUITO, TEF, HOMA2-B%, CP/G, CP/GCr, and BETA-2. The area under the ROC (AUROC) curves were compared to the AUROC's for beta score and 90-minute MMTT glucose concentration in order to determine which of the surrogate indices detected the outcome with sufficient discrimination. Youden's index was calculated (specificity + sensitivity − 1) and used to select the optimal cutoffs for each index. For these analyses (*t* tests and ROC analysis), the bootstrap [17] was used to account for repeated measurements by re-sampling patients. In the short-term (ST) group, Kaplan-Meier curves were made for duration of insulin-independent survival according to optimal cutoffs for each of the 6 surrogate indices on day 75. The Andersen-Gill [18] Cox model was fit to accommodate multiple events. Throughout, a $P < .05$ was considered statistically significant. The statistical analyses were performed using the Statistica 12.0 (StatSoft, Kraków, Poland) and Stata 14.0 (StataCorp LLC, College Station, Texas) software packages.

3 | RESULTS

Cohort 1: The long-term (LT) follow-up group included 4 subjects with type 1 diabetes, 1 male and 3 females, aged 42, 36, 51, and 48 years at the time of first transplant, with a follow-up of 140, 131, 119, and 81 months, respectively. All received a second and third islet infusion

when they required insulin support after previous transplant for optimal glucose control.[19] Immunosuppression was modified whenever clinically necessary. These patients received an average islet mass of 445,000 islet equivalent units (IEQ) (225-719 kIEQ) and 7400 IEQ/kg (4400-11 000 IEQ/kg). Each subject was scheduled to have a MMTT every 6 months as per protocol. Overall, 47 MMTTs were performed: 41 tests when patients were insulin independent, and 6 tests in patients requiring insulin support. Cohort 2: The ST follow-up group consisted of 13 type 1 diabetic subjects (4 males and 9 females) at the median age of 45 years (interquartile range [IQR] 36-51) at the time of first islet transplant with median follow-up of 33 months (IQR 30-38). All received a second ITx within the first year after the initial ITx and third islet infusion after the first year, when they required insulin support after second transplant for optimal glucose control. These patients received an average islet mass of 459 000 IEQ (269-689 kIEQ) and 6809 IEQ/kg (4660-9993 IEQ/kg). Each subject underwent a MMTT as per protocol after ITx on day 75, at 12 months, and annually. Overall, 54 MMTT were performed: 38 when patients were insulin independent, and 16 when insulin support was required. In 8 cases it was impossible to calculate HOMA-2B% as either glucose or C-peptide values exceeded range limits accepted by the HOMA-2 calculator (required range for glucose from 54.1 to 450.5 mg/dL and for C-peptide from 0.2 to 3.5 nmol/L).

TABLE 3 Relationships between each of the surrogate indices (SUITO, TEF, HOMA2-B%, CP/G, CP/GCr, BETA-2 score) and the reference indices of beta cell function derived from MMTT and beta score

LT + ST group N = 17 (101 MMTT)				
	with beta score		with MMTT 90-min glucose	
Correlation	*r*	*P*	*r*	*P*
SUITO	.68	<.001	−.60	<.001
TEF	.18	.33	−.06	.85
HOMA2-B%	.68	<.001	−.56	<.001
CP/G	.54	<.001	−.60	<.001
CP/GCr	.41	.003	−.52	<.001
BETA 2	.72	<.001	−.76	<.001

BETA 2, BETA-2 score; CP/G, C-peptide/glucose ratio; CP/GCr, C-peptide/glucose creatinine ratio; HOMA2-B%, homeostasis model assessment; LT, long term; MMTT, mixed meal tolerance test; ST, short term; SUITO, secretory unit of islet transplant objects; TEF, transplant estimated function.

TABLE 4 AUROC of the surrogate indices for the detection of need for insulin support

	N = 17 (101 MMTT)			
LT + ST group	AUROC 95% CI		*P* value	Cutoff
SUITO	0.840	(0.697-0.983)	<.001	<27.6
TEF	0.583	(0.329-0.837)	.52	<0.21
HOMA2-B%	0.755	(0.569-0.941)	.007	<46.4
CP/G	0.855	(0.712-0.998)	<.001	<0.98
CP/GCr	0.848	(0.722-0.973)	<.001	<0.93
BETA 2	0.900	(0.808-0.992)	<.001	<12.9
Beta score	0.884	(0.774-0.995)	<.001	<7
MMTT 90-min glc	0.849	(0.759-0.939)	<.001	>159

AUROC, area under receiver operating curve; BETA 2, BETA-2 score; CI, confidence interval; CP/G, C-peptide/glucose ratio; CP/GCr, C-peptide/glucose creatinine ratio; glc, glucose; HOMA2-B%, homeostasis model assessment; LT, long term; MMTT, mixed meal tolerance test; ST, short term; SUITO, secretory unit of islet transplant objects; TEF, transplant estimated function.

3.1 | Relationship between reference and surrogate indices

Four indices (SUITO, CP/G, HOMA 2-B%, and BETA-2) were modestly/well correlated with both beta score and MMTT 90-minute glucose (Table 3) with the magnitude of the correlation coefficients in the range 0.54 to 0.76. Of note, SUITO and BETA-2 showed the strongest correlation with the reference methods. CP/GCr showed less correlation and TEF performed worst, with little associations.

3.2 | Surrogate indices and detection of need for insulin support and glucose intolerance

The AUROC curve analyzed for all surrogate indices showed slightly heterogeneous results, with no discriminative ability of insulin independence vs dependence for TEF (AUC=0.58, $P = .52$), borderline performance for HOMA2-B%, acceptable performance of SUITO, CP/G, and CP/GCr, and excellent discriminative ability for BETA-2 (AUC=0.90, $P < .001$) (Table 4, Figure 1A). These findings mirrored the results of the correlation analyses. The AUROCs for SUITO, CP/G, CP/GCr, and BETA 2 were similar to those for the reference values, beta score, and MMTT 90-minute glucose. When we analyzed the ability of the surrogate indices to detect glucose intolerance in both groups, again all but TEF had a very good performance (Table 5, Figure 1B).

3.3 | Surrogate indices and detection of ITx success as defined by the Igls classification of beta cell graft function

All surrogate indices, apart from TEF and HOMA2-B%, showed excellent performance in identifying ITx success as defined by the Igls classification of beta cell graft function with AUROCs >0.8 and $P < .001$ (Table 6). The AUROCs for BETA-2, SUITO, and CP/G did not differ significantly when compared to AUROC for beta score or MMTT 90-minute glucose, but we found a significant difference in the case of TEF (poorer performance).

3.4 | Surrogate indices and predicting return to exogenous insulin therapy

In the ST group:

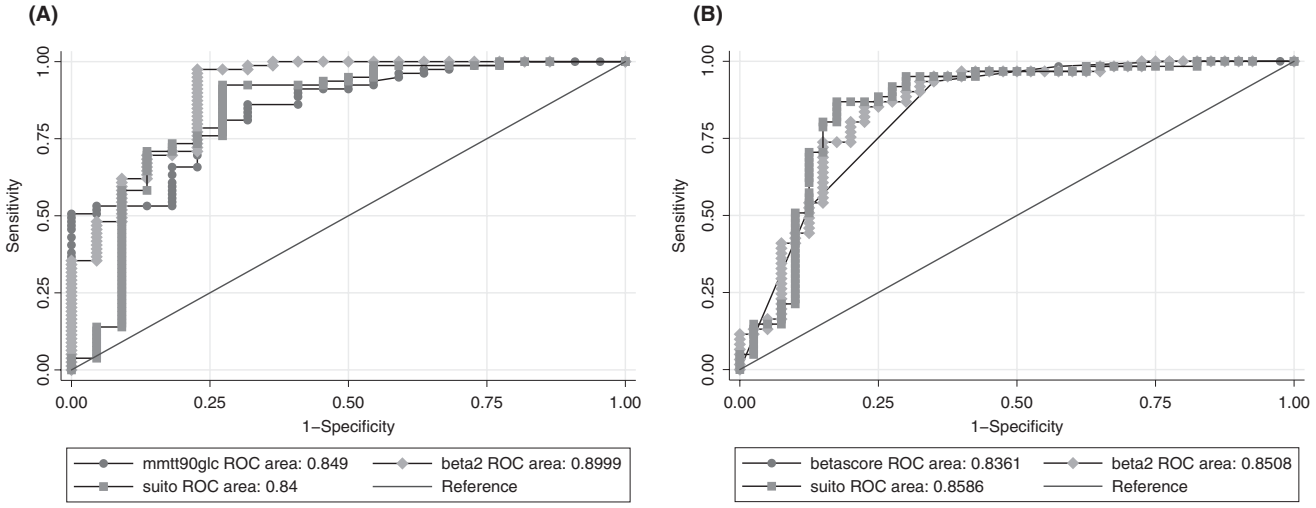

FIGURE 1 Receiver operating characteristic (ROC) curves of (A) 90-min MMTT glucose, BETA 2, and SUITO for the detection of need for insulin support, (B) beta score, BETA 2, and SUITO for the detection of glucose intolerance (90-min MMTT glc ≥ 144 mg/dL) in LT+ST group. BETA 2, BETA-2 score; LT, long term; MMTT, mixed meal tolerance test; ROC, receiver operating characteristic; ST, short term; SUITO, secretory unit of islet transplant objects

TABLE 5 AUROC of the surrogate indices for the detection of glucose intolerance (MMTT 90-min glucose ≥ 144 mg/dL)

	N = 17 (101 MMTT)			
LT+ST group	AUROC 95% CI		*P* value	Cutoff
SUITO	0.859	(0.758-0.959)	<.001	<41.8
TEF	0.541	(0.400-0.681)	.57	<0.21
HOMA2-B%	0.771	(0.661-0.881)	<.001	<64.0
CP/G	0.834	(0.734-0.935)	<.001	<1.05
CP/GCr	0.782	(0.669-0.895)	<.001	<1.08
BETA 2	0.851	(0.764-0.937)	<.001	<17.8
Beta score	0.836	(0.735-0.937)	<.001	<7

AUROC, area under receiver operating curve; BETA 2, BETA-2 score; CI, confidence interval; CP/G, C-peptide/glucose ratio; CP/GCr, C-peptide/glucose creatinine ratio; HOMA2-B%, homeostasis model assessment; LT, long term; MMTT, mixed meal tolerance test; ST, short term; SUITO, secretory unit of islet transplant objects; TEF, transplant estimated function.

TABLE 6 AUROC of the surrogate indices for the detection of ITx success as defined by the Igls classification of beta cell graft function

	N = 17 (101 MMTT)			
LT group + ST group	AUROC 95% CI		*P* value	Cutoff
SUITO	0.833	(0.647-1)	<.001	>29.4
TEF	0.586	(0.296-0.875)	.86	>0.19
HOMA2-B%	0.712	(0.393-1)	.19	>44.6
CP/G	0.858	(0.648-1)	<.001	>1.00
CP/GCr	0.844	(0.683-1)	<.001	>0.93
BETA 2	0.899	(0.783-1)	<.001	>12.5
Beta score	0.973	(0.945-1)	<.001	≥7
MMTT 90-min glc	0.945	(0.884-1)	<.001	<188

AUROC, area under receiver operating curve; BETA 2, BETA-2 score; CI, confidence interval; CP/G, C-peptide/glucose ratio; CP/GCr, C-peptide/glucose creatinine ratio; glc, glucose; HOMA2-B%, homeostasis model assessment; ITx, islet allotransplantation; LT, long term; MMTT, mixed meal tolerance test; ST, short term; SUITO, secretory unit of islet transplant objects; TEF, transplant estimated function.

1. The ability of each assay performed on day 75 post ITx to predict the return to exogenous insulin therapy at 1 year post ITx.

Of all the surrogate tools on day 75, the BETA-2, SUITO, CP/G, and HOMA2-B% seemed equally good predictors of insulin independence 1 year after ITx (with AUROCs > 0.808-0.942, $P < .001$), while CP/GCr (AUROC 0.683, $P = .09$) and TEF (AUROC 0.408, $P = .83$) were unreliable. The AUROCs for BETA-2, SUITO, CP/G, and HOMA2-B% did not differ significantly when compared to AUROC for MMTT 90-min glucose (Table 7).

2 Comparison of fasting glucose, MMTT 90-minute glucose, and the 6 surrogate indices estimated on day 75 between insulin dependent and insulin-free patients 1 year after ITx.

The values of BETA-2, SUITO, CP/G, and HOMA2-B% estimated on day 75 differed significantly between patients who were on vs off insulin 1 year after ITx ($P < .005$). CP/GCr and TEF did not differ significantly between patients with a metabolic state of acceptable blood glucose control without the need for insulin supplementation vs those requiring insulin support ($P = .13$ and $P = .29$, respectively).

3 The insulin free persistence (survival) according to the surrogate indices measured on day 75 post ITx (above vs below the cutoff value) (Kaplan-Meier analysis).

Insulin-free persistence (survival) differed significantly between patients whose BETA 2 (Figure 2A), SUITO, CP/G, CP/GCr and

TABLE 7 AUROC of the surrogate indices estimated on d 75 post ITx for the prediction of insulin independence at 1 y post ITx in the ST group (N = 13; 22 MMTT)

	AUROC 95% CI		*P* value	Cutoff
SUITO	0.933	(0.836-1)	<.001	>43.0
TEF	0.408	(0.223-0.594)	.83	0.77
HOMA2-B%	0.917	(0.763-1)	<.001	>63.0
CP/G	0.808	(0.627-1)	<.001	>1.20
CP/GCr	0.683	(0.473-0.894)	.089	>1.14
BETA 2	0.942	(0.869-1)	<.001	>19.0
Beta score	0.854	(0.704-1)	<.001	≥7
MMTT 90-min glc	0.883	(0.738-1)	<.001	<117

AUROC, area under receiver operating curve; BETA 2, BETA-2 score; CI, confidence interval; CP/G, C-peptide/glucose ratio; CP/GCr, C-peptide/glucose creatinine ratio; glc, glucose; HOMA2-B%, homeostasis model assessment; ITx, islet allotransplantation; MMTT, mixed meal tolerance test; ST, short term; SUITO, secretory unit of islet transplant objects; TEF, transplant estimated function.

HOMA2-B% values measured on day 75 post ITx were below and over the cutoff. However, TEF measurement on day 75 did not affect the long-term prognosis (Figure 2B).

4 Surrogate indices on day 75 post ITx and their prediction of ITx success based on the Igls classification of beta cell graft function at 1 year post ITx.

The results mirrored those reported for the loss of insulin independence that was anticipated at 1 year. Of all the surrogate tools on day 75, BETA-2, SUITO, CP/G, and HOMA2-B% seemed equally good predictors of ITx success 1 year after ITx as defined by the Igls classification (with AUROCs > 0.848-0.964, *P* < .001), while TEF (AUROC 0.33, *P* = .96) was unreliable (Table 8).

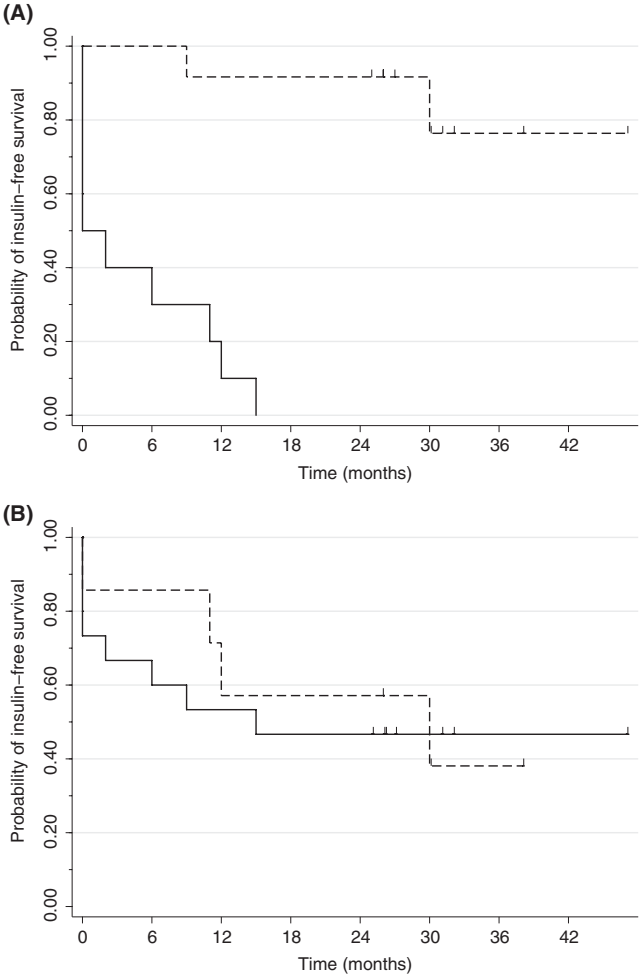

FIGURE 2 Kaplan-Meier insulin-free survival curve (A) according to BETA 2 value on day 75 post ITx above (dashed line) vs under (solid line) the cutoff of 19.0 (*P* = .003), (B) according to TEF value on day 75 post ITx above (dashed line) vs under (solid line) the cutoff of 0.77 (*P* = .34). BETA 2, BETA-2 score; ITx, islet autotransplantation; TEF, transplant estimated function

3.5 | Factors affecting the accuracy of surrogate indices

We did not find any consistent patterns when the influence of BMI and gender was analyzed.

4 | DISCUSSION

Despite advancements in islet procurement and immunosuppression that have increased islet transplant survival, graft function still progressively declines, and the duration of insulin independence is not permanent. Therefore, an unmet need for techniques that assess beta cell function and can be used both in a controlled experimental setting as well as in everyday clinical practice remains to be validated to allow for properly guided decision-making. It is of great importance to be able to detect early graft function decline to rescue the remaining islets from complete loss and a return to "brittle" type 1 diabetes.

Fasting glucose and C-peptide concentrations are the most elementary markers of beta cell function and despite many limitations both are the mainstay of a number of mathematical formulas created to estimate beta cell function after ITx.

The practical aim of this study was to choose the best equation that could assist in everyday clinical decision-making. Our results indicate that BETA-2, CP/G, and SUITO could safely be implemented in the evaluation and management of ITx recipients. All 3 indices showed invariable and reliable performance, not only as markers of current metabolic status, but also predicting at least the short-term future of islet allograft function. Even though BETA-2 did not outperform beta score as in the study by Forbes et al, it still has a clinical advantage of being calculated from a single fasting blood sample.[13] Of note, we found similar cutoff values effective for BETA 2 as proposed in the study from Edmonton: 12.9 for insulin independence and 17.8 for glucose intolerance, respectively.[13] Likewise, in the case of SUITO index, scores above 26 detected insulin independence in the development

TABLE 8 AUROC of the surrogate indices estimated on d 75 post ITx in the ST group for the prediction of ITx success at 1 y post ITx as defined by the IgIs classification of beta cell graft function (N = 13; 22 MMTT)

	AUROC 95% CI		*P* value	Cutoff
SUITO	0.938	(0.834-1)	<.001	>43.0
TEF	0.331	(0.136-0.525)	.96	[a]
HOMA2-B%	0.943	(0.845-1)	<.001	>68.8
CP/G	0.848	(0.655-1)	<.001	>1.20
CP/GCr	0.830	(0.598-1)	.005	>1.14
BETA 2	0.964	(0.905-1)	<.001	>19.0
Beta score	0.879	(0.724-1)	<.001	≥7
MMTT 90-min glc	0.911	(0.809-1)	<.001	<125

AUROC, area under receiver operating curve; BETA 2, BETA-2 score; CI, confidence interval; CP/G, C-peptide/glucose ratio; CP/GCr, C-peptide/glucose creatinine ratio; glc, glucose; HOMA2-B%, homeostasis model assessment; ITx, islet allotransplantation; MMTT, mixed meal tolerance test; ST, short term; SUITO, secretory unit of islet transplant objects; TEF, transplant estimated function.
[a]Cannot be calculated.

cohort described by Takita et al, while in our study the cutoff value was similar (ie 27.6).[1] Also, in the case of CP/G ratio in the study by Faradji et al, the odds of having lower CP/G (<1.0) were about 4 times greater with exogenous insulin use; again in our study the cutoff for insulin independence was 0.98.[12] With reproducible and comparable performance, the main advantage of BETA-2, SUITO, and CP/G is that these indices can be calculated utilizing only the fasting values of C-peptide and glucose, which are easier and more frequently obtained than stimulation tests (eg MMTT), allowing for closer monitoring and alterations in management for improved outcomes.

As TEF was designed to quantitate insulin secretion, it does not provide an integrated measure of the metabolic status of the transplant recipient, which also encompasses insulin sensitivity.[9,10] This would account for the poor performance of TEF in our study.

CP/GCr was designed to assess islet graft dysfunction in patients with renal disease. Creatinine is the most commonly used endogenous glomerular filtration marker in clinical practice.[12] Since there are many physiologic and iatrogenic determinants of the creatinine serum level, it seems more plausible to use estimated glomerular filtration rate for the purpose of the correction. So far this index has not been validated in patients with impaired kidney function. Because all patients from both of our study populations had good kidney function, we were also unable to do so. In our population it showed modest performance, with no additional benefit.

Since HOMA2-B% cannot be applied in patients with blood glucose and C-peptide outside the set range, this limits its utility.[11] In 8 patients HOMA2-B% could not be evaluated for the aforementioned reason. This could have resulted in a substantial bias and influenced the overall performance.

One of the limitations of the study is that it was based on results from a single center with a particular strategy for patient clinical management as well as islet isolation and transplantation procedures. For the same reason, the number of patients included was limited. The results may not be generalizable to other transplant populations, which may have different approaches to retransplant, but we focused on insulin independence since most testing was performed in insulin-independent subjects. Other studies will likely be necessary to more accurately determine the utility of indices where function is lower. Despite these limitations, we believe that our results have important clinical value. To our knowledge, this is the first study that undertook a robust external assessment of all currently available surrogate indices based on a single fasting blood sample using a fully independent and external validation cohort. We emphasize the need for independent validation of our findings in several populations before clinicians place great confidence in their routine use. The use of surrogate indices for autologous islet recipients is currently under investigation.

In conclusion, the 6 estimating equations showed different accuracy in identifying islets allograft dysfunction and anticipating loss of insulin independence at 1 year with reference to more logistically challenging MMTT and beta score. BETA 2, SUITO, and CP/G seem to constitute valuable, simple, and reliable methods for the evaluation of beta cell function. Therefore they should be useful in care management.

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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*.

ORCID

Justyna E. Gołębiewska http://orcid.org/0000-0001-5346-8369
Piotr Witkowski http://orcid.org/0000-0002-4459-6673

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