学位論文

Short-term recovery of meal-responded insulin secretion is associated with future glycemic control in type 2 diabetes

令和 5 年度

富山大学　医学薬学教育部博士課程

生命・臨床医学専攻

内科学（第一）講座

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Abstract

Aims/Introduction: Endogenous insulin secretion could be recovered by improving hyperglycemia in patients with type 2 diabetes (T2D). This study aimed to investigate the association between short-term recovery of insulin secretion during hospitalization and clinical background or future glycemic control in patients with T2D.

Materials and Methods: A total of 127 patients with T2D were included. The recovery of endogenous insulin secretion was determined using the following indices: index-A: Fasting C-peptide index (CPI) at discharge – fasting CPI on admission, index-B: Postprandial CPI at discharge – postprandial CPI on admission, and index-C:Δ C-peptide immunoreactivity (CPR) (postprandial CPR − fasting CPR) at discharge – ΔCPR on admission. I examined the associations of each index with clinical background and future glycemic control measured by glycosylated hemoglobin (HbA1c) and continuous glucose monitoring.

Results: Using the index A, the age was significantly younger, while BMI and visceral fat area were significantly higher in the high-recovery group than in the low-recovery group. Changes in HbA1c levels were significantly greater at 6 and 12 months in the high-recovery group in the analysis of index-C. The receiver operating characteristic curve analysis identified the index-B and index-C as indicators to predict HbA1c < 7.0% at 6 months after discharge. Furthermore, the index-C was positively correlated with the time in the target glucose range and inversely correlated with the standard deviation of glucose at 3 and 12 months after discharge.

Conclusions: Short-term recovery of meal-responded insulin secretion during hospitalization, evaluated with the index-C, may predict future glycemic control.

Introduction

Type 2 diabetes (T2D) is caused by the insufficiency of insulin action as a consequence of both impaired pancreatic beta cell (β-cell) function and insulin resistance in peripheral tissues (1,2). In the diabetic state, nuclear expression of several pancreatic transcription factors is reduced due to oxidative stress. Additionally, decreased expression of incretin receptors on the β-cell membrane due to hyperglycemia causes decreased insulin secretion (3,4). However, how glucose exerts these effects is poorly understood (5). In a clinical setting, Ryan et al. demonstrated that prolonged appropriate glycemic control and preserved pancreatic beta cell function were achieved by eliminating glucose toxicity due to short-term intensive insulin therapy in their hospital (6). Ilkova et al. also reported that short-term intensive insulin therapy enabled long-term glycemic control without medication in patients with type 2 diabetes (7).

In patients with T2D, evaluating pancreatic β-cell function is crucial to determine treatment plans. Several indices, including the C-peptide index (CPI), the secretory units of islets in transplantation (SUIT), and the homeostatic model assessment beta cell function (HOMA-β) have been established as indicators of pancreatic β-cell function (8-10). Iwata et al. reported that the SUIT and fasting CPI during hospitalization were useful for predicting the requirement for insulin therapy at 12 months after discharge in patients with T2D. In contrast, Saisho et al. reported that postprandial CPI during hospitalization could be a predictor of the requirement for insulin treatment around 4.5 years after discharge (11,12). In addition, lower C-peptide immunoreactivity (CPR) levels were associated with a higher prevalence of microvascular complications, suggesting that pancreatic β-cell function also affects the onset of diabetic complications (13). These studies used CPR or CPI measured after glucose-lowering therapy to make predictions.

However, no previous studies have used short-term recovery of endogenous insulin secretion, indicated by the improvement of glucose toxicity, to predict glycemic control after discharge in patients with T2D.

This study aimed to explore the clinical background, including metabolic parameters, that affect the short-term recovery of endogenous insulin secretion during hospitalization in patients with T2D. I used fasting and postprandial CPI at admission and discharge to measure outcomes. Furthermore, I investigated the associations between the short-term recovery of endogenous insulin secretion and glycemic and other metabolic controls after discharge. This dissertation was based on an original paper submitted to the Journal of Diabetes Investigation (14).

Material and methods

Study participants and ethics

The background of patients admitted for glycemic control includes those who have poor glycemic control while walking out of my hospital or a family doctor, those who were first diagnosed with diabetes by a physical examination, and those who have poor glycemic control before surgery for other diseases. A total of 317 patients, who were admitted from Merch 2017 to December 2021 in Toyama University Hospital for glycemic control, were recruited to this study. After 190 patients were excluded according to the exclusion criteria described below, 127 patients with T2D were participated in the study. Ten out of 127 participants were also included in the prospective study. The Patients whose fasting and postprandial (2 hours) plasma glucose (PG) and serum CPR levels were measured at admission and discharge were included. To avoid the modification of CPR values due to accompanying physical conditions, the exclusion

criteria were defined as follows: 1) patients with impaired renal function (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2), 2) patients who received anti-cancer chemotherapy or systemic administration of steroids, 3) patients with pancreatitis or those who underwent pancreatic resection, 4) patients with liver cirrhosis, and 5) patients who underwent gastrectomy. All procedures performed were in accordance with the 1964 Helsinki Declaration and its later amendments and the "Ethical Guidelines for Medical and Health Research Involving Human Subjects" published by the Ministry of Health, Labor, and Welfare of Japan. The study protocol was approved by the ethical committee of Toyama University Hospital (Study No. R2021003). Patients who participated in the retrospective study had the opportunity to object to using their data for scientific research, but none of the patients did. Written informed consent was obtained from the patients who participated in the prospective study.

Study design and data collection

The present study had an observational, single-center design. The total amount of calories in the diet provided during hospitalization was calculated as follows; standard body weight was multiplied by 28-30 kcal, including 60-64% carbohydrates. I retrospectively investigated the relationships between the indices related to the recovery of endogenous insulin secretion described below and clinical parameters to identify those parameters that influence short-term recovery. The 'short-term' was defined as the period between the measurement of CPI on admission and that at discharge, with a mean duration of 10.9 ± 4.5 days. In addition, to investigate whether the short-term recovery of endogenous insulin secretion during hospitalization could predict glycemic controls after discharge, I retrospectively studied the association between those indices and metabolic parameters,

including glycosylated hemoglobin (HbA1c), at 3, 6, and 12 months after discharge. For the patients who were admitted to my hospital after January 2021, I also prospectively investigated the association between the short-term recovery of insulin secretion during hospitalization and metabolic parameters, including glucose fluctuation measured by intermittently-scanned continuous glucose monitoring (isCGM; FreeStyle Libre pro, Abbott Laboratories, IL, USA) up to 12 months after discharge. In the analysis using isCGM, I obtained average glucose levels, standard deviation (SD), time in targeted glucose range (TIR: 70-180 mg/dL), time above targeted glucose range (TAR: > 180 mg/dL), time below targeted glucose range (TBR: < 70 mg/dL) using the data from 5 days measurement, except for the data from the first 2 days of the measurement. Indices used to evaluate the short-term recovery of endogenous insulin secretion during hospitalization were defined as follows: index-A: fasting CPI at discharge − fasting CPI on admission, index-B: postprandial CPI at discharge − postprandial CPI on admission, and index-C: ΔCPR (postprandial CPR − fasting CPR) at discharge − ΔCPR (postprandial CPR− fasting CPR) on admission. Serum CPR levels were measured using a chemiluminescent enzyme immunoassay (CLEIA). The CPI was calculated as follows: CPR (ng/mL)/PG (mg/dL) × 100. Fasting and postprandial (2 hours) CPI before and 2 hours after meals were obtained on admission and at discharge.

Sample size calculations

The sample size was calculated based on HbA1c values. It was found that a sample size of 75 patients would be sufficient to detect a 1.0% difference in HbA1c as a glycemic parameter after discharge, assuming a standard deviation of 0.95, a = 0.05, and a power of 99%. Considering the cases of dropout, a total of 127 patients were recruited. These

calculations were conducted using JMP software for Macintosh, Version Pro 15 (SAS Institute, NC, USA).

Statistical analysis

The correlations between endogenous insulin secretion recovery indices and various clinical parameters were analyzed using Spearman's correlation coefficient. I also compared the value of each clinical indicator between the group that showed low recovery of the endogenous insulin secretion (low-recovery group) and the group that showed high recovery of the secretion (high-recovery group). The low-recovery and high-recovery groups were classified using the median endogenous insulin secretion recovery indices. The analysis of Wilcoxon rank sum test, chi-square test, multivariate logistic regression analysis were used for analysis between bivariate variables, depending on the distribution of the variables. In the multivariate logistic regression analysis, each model was set up by selecting independent variables after examining collinearity among items that were significantly different in the high-recovery group for each index. The repeated ANOVA test was employed to determine the association between endogenous insulin secretion recovery indices and glycemic parameters, including HbA1c, after discharge. The correlations between endogenous insulin secretion recovery indices and the factors related to glucose levels and fluctuation evaluated with isCGM were analyzed using Spearman's correlation coefficient. Results with P-values < 0.05 were considered statistically significant. All statistical analyses were conducted using JMP software for Macintosh, Version Pro 15 (SAS Institute, NC, USA).

Results

Clinical factors associated with short-term recovery of endogenous insulin secretion during hospitalization

Table 1 shows the clinical characteristics of the participants. The age on admission was 63 (range, 51-73 years), diabetes duration was 10 (range, 5-18 years), HbA1c level on admission was 9.9 (range, 8.8-11.4%), and BMI on admission was 26.0 (range, 23.1-29.1 kg/m^2); the data are presented as median (interquartile range [IQR]).

To identify clinical factors associated with short-term recovery of endogenous insulin secretion, I compared clinical factors between T2D patients with low recovery and those with high recovery of the secretion during their hospitalization using index-A, index-B, and index-C. The group with low recovery and that with high recovery of endogenous insulin secretion were divided using the median of the index-A (median: 0.39), B (1.08), and C (0.50).

In the analysis using the index-A, the age on admission (60 [51-69] vs. 69 [53-75] years, P = 0.021) was significantly lower and the proportion of women (55 vs. 27%, P = 0.002) significantly higher in the high-recovery group than in the low-recovery group. Furthermore, peak BMI (30.6 [26.8-35.0] vs. 29.1 [25.1-31.4] kg/m^2, P = 0.023) and BMI on admission (26.6 [23.9-30.2] vs. 24.7 [21.5-27.9] kg/m^2, P = 0.008) were significantly higher in the high-recovery group than in the low-recovery group, as were the waist circumferences (98 [88-109] vs. 93 [84-99] cm, P = 0.010), visceral fat area (160.2 [113.9-203.2] vs. 136.6 [87.7-183.1] cm^2, P = 0.047), and subcutaneous fat area (210.2 [134.8-265.3] vs. 146.7 [94.3-181.1] cm^2, P < 0.001). Additionally, in the low-recovery group, a higher percentage of patients were administered sulfonylureas (25 vs. 8%, P = 0.008) and DPP-4 inhibitors (73 vs. 52%, P = 0.013) on admission than in the high-recovery group.

However, a higher percentage of patients in the high-recovery group were administered SGLT2 inhibitors (22 vs. 6%, P = 0.012) on admission and added GLP-1 receptor agonists during hospitalization (33 vs. 8%, P = 0.001) than in the low-recovery group (**Table 1**). In multivariate logistic regression analysis using the index-A, women (odds ratio 0.264 [95%CI, 0.083-0.838], P = 0.024), the higher visceral fat area (odds ratio 1.008 [95% CI, 1.001-1.014], P = 0.020), a lower percentage of patients who were administered sulfonylureas on admission (odds ratio 0.106 [95% CI, 0.021-0.532], P = 0.006) and a higher percentage of patients who added GLP-1 receptor agonist during hospitalization (odds ratio 5.279 [95% CI, 1.434-19.436], P = 0.012) were significant factors in the high index-A recovery group (**Table 2, Model 3**).

In the analysis using the index-B, the age on admission (62 [48-71] vs. 65 [53-76] years, P = 0.027) was significantly lower, and BMI on admission (26.6 [23.6-30.1] vs. 25.3 [21.9-27.9] kg/m^2, P = 0.022) significantly higher in the high recovery group than in the low-recovery group. Consistent with the analyses using the index-A, visceral fat area (165.9 [111.4-218.1] vs. 138.4 [87.6-167.4] cm^2, P = 0.022) and subcutaneous fat area (182.4 [125.9-260.4] vs. 154.0 [101.8-211.1] cm^2, P = 0.038) were significantly higher in the group with high-recovery of postprandial CPI than in the low-recovery group. Serum levels of triglycerides (TG) (135 [108-184] vs. 105 [79-139] mg/dL, P = 0.001) and γ-GTP (40 [23-62] vs. 22 [17-43] U/L, P = 0.001) were also significantly higher in the high-recovery group than in the low-recovery group. The percentage of patients who received sulfonylureas (24 vs. 9%, P = 0.029) and glinides (16 vs. 2%, P = 0.004) on admission was higher in the low-recovery group. The percentages of patients who were administered biguanides (34 vs. 16%, P = 0.015) and sodium-glucose cotransporter-2 (SGLT-2) inhibitors (34 vs. 17%, P = 0.030) during hospitalization were higher in the

high-recovery group (**Table 3**). In multivariate logistic regression analysis using the index-B, the higher visceral fat area (odds ratio 1.006 [95% CI, 1.000-1.012], P = 0.035) and a lower percentage of patients who were administered sulfonylureas (odds ratio 0.260 [95% CI, 0.083-0.809], P = 0.020) and glinide (odds ratio 0.081 [95% CI, 0.001-0.694], P = 0.022) on admission were significant factors in the high index-B recovery group (**Table 4, Model 3**).

In the high-recovery group of the index-C, HbA1c on admission [10.6 (9.3-12.0) vs. 9.6 (8.5-10.7) %, P = 0.004] and the percentages of patients who were administered biguanides [33 vs. 17 %, P = 0.036] and SGLT2 inhibitors [35 vs. 17 %, P = 0.023] were significantly higher than in the low-recovery group. The index-C analysis identified no associations between the short-term recovery of ΔCPR and age, BMI, or body fat distribution (**Table 3**). In multivariate logistic regression analysis using the index-C, only the higher value of HbA1c on admission (odds ratio 1.330 [95%CI, 1.066-1.660], P = 0.009) was a significant factor (**Table 5**). In addition, no significant differences in weight reduction during hospitalization were found between the two groups in the analyses using any of the indices (**Table 1,3**).

No significant differences in any of the indices were found between patients with fasting plasma glucose (FPG) levels less than 126 mg/dL at discharge and those with FPG levels equal to or greater than 126 mg/dL, indicating that the values of each index were not affected by glucotoxicity at discharge (**Table S1**).

Association between short-term recovery of endogenous insulin secretion during hospitalization and glycemic control after discharge

Next, I investigated the effect of short-term recovery of endogenous insulin secretion during hospitalization on glycemic control at 6 months and 12 months after discharge (**Figure. 1**). HbA1c levels were not significantly different between the low-recovery group and the high-recovery group after discharge using postprandial CPI at discharge and the indices A-C (**Figure. 1a, b, c, d**). I also compared changes in HbA1c levels from the time point of admission to 6 and 12 months after between the two groups (**Figure. 2**). In the analysis using postprandial CPI at discharge, the indices A and B, there were no significant differences in the changes in HbA1c levels up to 6 and 12 months after discharge between the two groups (**Figure. 2a, b, c**). In contrast, in the analysis using index-C, the change in the levels of HbA1c, was significantly greater at 6 months (-3.6 [-5.6 - -1.6] vs. -2.1 [-4.3 - -0.7] %, $P = 0.009$) and 12 months (-4.1 [-5.2 - -1.7] vs. -2.2 [-4.3 - -0.7] %, $P = 0.034$) in the high-recovery group than in the low-recovery group (**Figure. 2d**).

Indicators related to meal-responded insulin secretion during hospitalization predict glycemic control after discharge

Next, I determined which indicators that reflected recovery of endogenous insulin secretion during hospitalization could predict future glycemic control. Receiver operating characteristic (ROC) analyses were performed for the area under the curve (AUC) for each indicator, fasting and postprandial CPI, index-A, index-B, and index-C, for the prediction of HbA1c < 7.0% at 6 and 12 months after discharge (**Figure. 3**). The estimated cut-off points for postprandial CPI at discharge, the index-B, and index-C to predict HbA1c < 7.0% at 6 months after discharge were 3.79 (AUC 0.646, P = 0.030) (**Figure. 3g**), 1.49 (AUC 0.629, P = 0.026), (**Figure. 3k**), and 0.90 (AUC 0.621, P = 0.027) (**Figure.**

3m), respectively. In the ROC analysis, postprandial CPI on admission could not predict HbA1c < 7.0% at 6 months after discharge (**Figure. 3c**). The estimated cut-off points for postprandial CPI on admission and those at discharge to predict HbA1c < 7.0% at 12 months after discharge were 2.04 (AUC 0.679, P = 0.005) (**Figure. 3d**) and 3.65 (AUC 0.692, P = 0.003) (**Figure. 3h**), respectively. In the ROC analysis, the index-B (cut-off point 1.38, AUC 0.625, P = 0.070) (**Figure. 3l**) and the index-C (cut-off point 4.30, AUC 0.535, P = 0.251) (**Figure. 3n**) could not predict HbA1c < 7.0% at 12 months after discharge.

Correlation between the short-term recovery of endogenous insulin secretion during hospitalization and glucose variability after discharge

Finally, I prospectively examined the correlation between the factors related to glucose levels and fluctuation evaluated with isCGM and the indices A-C in the 10 patients with T2D at 3 and 12 months after discharge. While the index-A and B were not correlated with any CGM data (**Figure. S1 and S2**), index-C was positively correlated with TIR (r = 0.83, P = 0.005) and inversely correlated with SD of glucose levels (r = -0.67, P = 0.049) and TAR (r = -0.70, P = 0.037) at 3 months after discharge (**Figure. 4c, e, g**). Index-C tended to be inversely correlated with average glucose levels at 3 months after discharge (r = -0.60, P = 0.088) (**Figure. 4a**). Furthermore, at 12 months after discharge, index-C was positively correlated with TIR (r = 0.85, P = 0.016) and inversely correlated with SD (r = -0.86, P = 0.014) and TAR (r = -0.85, P = 0.016) (**Figure. 4d, f, h**). In addition, index-C tended to be inversely correlated with average glucose levels 12 months after discharge (r = -0.71, P = 0.071) (**Figure. 4b**). There were no significant correlations between index-C and TBR (**Figure. 4i, j**).

Discussion

The present study is the first to investigate how short-term recovery of endogenous insulin secretion due to blood glucose lowering therapy during hospitalization is associated with future glycemic control. In this study, several parameters were calculated based on serum CPR and plasma glucose levels, both of which reflect short-term recovery of endogenous insulin secretion, such as the difference between fasting and postprandial CPI on admission and discharge. Furthermore, the significance of these parameters has not been evaluated in previous studies.

I divided study participants into two groups, the group showing low recovery of endogenous insulin secretion (low-recovery group) and that showing high recovery of endogenous insulin secretion (high-recovery group). Using median values for indices-A, B, and C, I analyzed the correlation with various clinical factors. In a previous study investigating the correlation between the CPI and various clinical factors in 121 patients with T2D admitted for glycemic control, the postprandial CPI was inversely correlated with the duration of diabetes and the progression of diabetic retinopathy (15). In the present study, the patients in the high-recovery group were younger. They displayed higher BMIs, more visceral fat areas, and subcutaneous fat areas than those in the low-recovery group, according to the analysis using indices A and B. In addition, there was no correlation between weight reduction and any of the indices during hospitalization. This was probably because the length of hospitalization was too short to assess the impact of weight reduction.

Furthermore, in contrast to the result using index-A, those using index-B showed that the high-recovery group had significantly higher triglycerides and γ-GTP levels affected by obesity than those in the low-recovery group with the analysis of Wilcoxon

rank sum test. Kramer et al. reported that a decline in HOMA-IR might be a key determinant of improvement in β-cell function in response to short-term intensive insulin therapy, suggesting a fundamental contribution of insulin resistance to the reversible component of β-cell dysfunction in early T2D (16). According to these previous findings, it is speculated that patients with T2D with obesity require excessive additional insulin secretion to lower postprandial blood glucose levels due to their insulin resistance.

In addition, leptin production from adipocytes is suppressed under hyperglycemia. Improvement in glucose values leads to recovery of leptin production and enhances insulin action in skeletal muscle via activation of sympathetic nerves (17). This phenomenon was reported to be significantly more common in the obese group than in the non-obese group. The improvement in insulin sensitivity contributed to the improvement of glycemic control and significant recovery of endogenous insulin secretion by improving blood glucose levels (18).

In multivariate logistic regression analysis using the index-B, the significant factors were a lower percentage of patients who were administered sulfonylureas and glinide in the high-recovery group than in the low-recovery group. Whether this result is a cause or a consequence is difficult to assess, and all I can say is that there is an association between the meal-responsed endogenous insulin secretion and drugs to stimulate insulin secretion.

In order to investigate whether the indices related to the short-term recovery of endogenous insulin secretion influence glycemic control after discharge, I compared the levels of HbA1c between low- and high-recovery groups using the medians of indices-A, B, and C at 6 and 12 months after discharge. In the analyses using the index-C, the change in HbA1c level was significantly greater at 6 months and 12 months in the high-recovery

group than in the low-recovery group. In contrast, indices A and B were not associated with HbA1c after discharge. Sonoda et al. reported that fasting serum CPR levels and daily urinary CPR excretion could be indicators to predict glycemic control at 6 months after discharge (19). However, no reports have shown a relationship between the short-term recovery of endogenous insulin secretion and future glycemic control. My novel findings suggest that short-term recovery of meal-responded insulin secretion, rather than fasting insulin secretion, during hospitalization is an excellent indicator of glycemic control after discharge.

According to the ROC analyses, postprandial CPI at discharge, index-B, and index-C were significant predictors of HbA1c < 7.0% at 6 months after discharge. The postprandial CPI on admission and discharge were significant predictors of HbA1c < 7.0% at 12 months after discharge. In a previous report, postprandial CPI at admission was found to be an indicator to predict good glycemic control at 2 years after discharge (20). Since the short-term recovery of meal-responded insulin secretion during hospitalization has been identified as a novel indicator to predict good glycemic control after discharge, it is crucial to measure fasting and postprandial CPR and plasma glucose, not only during admission, but also at the time of discharge.

I also found the association between index-C, which reflects the short-term recovery of additional insulin secretion stimulated by food intake and the values related to glucose variability, including TIR, TAR, and SD of glucose levels, assessed by isCGM. A review of 18 articles reported strong correlations between HbA1c and the TIR in T2D. This review showed that HbA1c decreased by 0.8% when the TIR increased by 10% (21). Regarding the association between endogenous insulin secretion and CGM data, patients with type 1 diabetes with preserved fasting CPR levels displayed higher TIR and lower

TAR compared to those with deficient CPR levels (22). Since there have been no reports showing the correlation between the recovery of endogenous insulin secretion and future glucose variability assessed by CGM in T2D, my study may have a novel impact regarding the importance of meal-responded insulin secretion at discharge, not only on admission.

This study has several limitations. First, at the time of patient selection in this study, there was a large population selection bias due to a large number of exclusions in order to correctly assess CPR. Second, the intake of energy and nutrients when postprandial CPR levels were measured were not completely unified. In the future study, test meals will be desirable to evaluate meal-responded insulin secretion. Third, in examining which indicators that reflected recovery of endogenous insulin secretion during hospitalization could predict future glycemic control, the AUC for each indicator which performed by ROC analyses for the prediction of HbA1c < 7.0% at 6 and 12 months after discharge were relatively small . Fourth, a relatively small number of patients could be followed up for HbA1c, especially at 12 months after discharge (HbA1c: 72 cases). The number of patients participating in the prospective study using isCGM was small; only seven patients could be observed up to 12 months after discharge. However, it may be valuable to show significant associations between meal-responded insulin secretion and glucose variability, even with only a few participants.

In conclusion, short-term recovery of meal-responded insulin secretion during hospitalization may predict future glycemic control. Furthermore, my results suggest that the measurement of fasting and postprandial CPR not only on admission but also at the time of discharge is useful to understand metabolic state and to consider treatment options in T2D patients.

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Supporting information

Table S1. Comparison of each index between patients with fasting plasma glucose (FPG) levels at discharge less than 126 mg/dL and those with FPG levels equal to or more than 126 mg/dL

Figure S1. Correlation between the index-A and glucose variability evaluated using isCGM after discharge.

Figure S2. Correlation between the index-B and glucose variability evaluated using isCGM after discharge.

Figure legends

Figure 1. Comparison of HbA1c levels at 6 and 12 months after discharge between the low-recovery group and the high-recovery group of the indices related to endogenous insulin secretion. The two groups are divided using the median of each index. (a) Comparison of HbA1c levels in the analyses of postprandial CPI at discharge. (b) Comparison of HbA1c levels in the analyses using the index-A. (c) Comparison of HbA1c levels in the analyses using the index-B. (d) Comparison of HbA1c levels in the analyses using the index-C. Black triangles indicate the data in the low-recovery group and open circles indicate the data in the high-recovery group. HbA1c, glycosylated hemoglobin. Data were analyzed with repeated ANOVA.

Figure 2. Comparison of changes in HbA1c levels from the time point of admission to 6 and 12 months after discharge between the low-recovery group and the high-recovery group of the indices related to endogenous insulin secretion. (a) Comparison of the changes in HbA1c levels in the analyses of postprandial CPI at discharge. (b) Comparison of the changes in HbA1c levels in the analyses using the index-A. (c) Comparison of the changes in HbA1c levels in the analyses using the index-B. (d) Comparison of the changes in HbA1c levels in the analyses using the index-C. Black triangles indicate the data in the low-recovery group and open circles indicate the data in the high-recovery group. HbA1c, glycosylated hemoglobin. Data were analyzed with repeated ANOVA.

Figure 3. ROC curves of the indices related to endogenous insulin secretion during hospitalization to predict HbA1c < 7%. Cut-off values are calculated using the ROC

curves. (a,b) ROC curves analyzed using fasting CPI on admission to predict HbA1c < 7% at 6 months (a) and 12 months (b). (c,d) ROC curves analyzed using postprandial CPI on admission to predict HbA1c < 7% at 6 months (c) and 12 months (d). (e,f) ROC curves analyzed using fasting CPI at discharge to predict HbA1c < 7% at 6 months (e) and 12 months (f). (g,h) ROC curves analyzed using postprandial CPI at discharge to predict HbA1c < 7% at 6 months (g) and 12 months (h) after discharge. (i,j) ROC curves analyzed using index-A to predict HbA1c < 7% at 6 months (i) and 12 months (j) after discharge. (k,l): ROC curves analyzed using index-B to predict HbA1c < 7% at 6 months (k) and 12 months (l) after discharge. (m,n): ROC curves analyzed using index-C to predict HbA1c < 7% at 6 months (m) and 12 months (n) after discharge. ROC, receiver operating characteristic; AUC, area under the ROC curve; F-CPI, fasting C-peptide index; P-CPI: postprandial C-peptide index. Data were analyzed with logistic regression analysis.

Figure 4. Correlation between the index-C and glucose variability evaluated using isCGM after discharge. (a,b) Correlation between average glucose levels at 3 months (a) and at 12 months (b) after discharge and index-C. (c,d) Correlation between standard deviation at 3 months (c) and at 12 months (d) after discharge and index-C. (e,f) Correlation between TIR at 3 months (e) and at 12 months (f) after discharge and index-C. (g,h) Correlation between TAR at 3 months (g) and at 12 months (h) after discharge and index-C. (i,j) Correlation between TBR at 3 months (i) and at 12 months (j) after discharge and index-C. TIR, time in targeted glucose range (TIR: 70-180 mg/dL); TBR, time below targeted glucose range (TBR: < 70 mg/dL); TAR, time above targeted

glucose range (TAR: > 180 mg/dL). Data were analyzed with Spearman's correlation coefficient.

Table 1. Comparison of clinical characteristics between T2D patients with low recovery and those with high recovery of index-A

	Total	Index-A		P-value
		Low-recovery group	High-recovery group	
Number	127	63	64	NA
Age (years)	63 (51-73)	69 (53-75)	60 (51-69)	0.021
Male/Female	75/52	46/17	29/35	0.002
Duration of T2D (years)	10 (5-18)	10 (6-18)	8 (4-18)	0.133
Family history of diabetes (%)	65	71	59	0.154
History of smoking (%)	54	64	45	0.040
History of alcohol intake (%)	35	43	27	0.054
BMI at the age of 20 years (kg/㎡)	22.2 (20.1-25.5)	23.2 (20.4-25.2)	21.3 (19.8-26.3)	0.142
Peak BMI (kg/㎡)	29.4 (26.4-32.8)	29.1 (25.1-31.4)	30.6 (26.8-35.0)	0.023
BMI on admission (kg/㎡)	26.0 (23.1-29.1)	24.7 (21.5-27.9)	26.6 (23.9-30.2)	0.008
BMI at discharge (kg/㎡)	24.8 (22.6-28.4)	24.1 (21.1-26.5)	25.9 (23.6-29.8)	0.003
Changes in weight reduction during hospitalization (kg)	2.1 (1.2-3.0)	1.8 (1.1-3.0)	2.3 (1.3-3.0)	0.304
Waist circumference (cm)	95 (87-103)	93 (84-99)	98 (88-109)	0.010
Visceral fat area (cm^2)	148.0 (98.6-194.8)	136.6 (87.7-183.1)	160.2 (113.9-203.2)	0.047
Subcutaneous fat area (cm^2)	166.6 (110.7-227.9)	146.7 (94.3-181.1)	210.2 (134.8-265.3)	< 0.0001
HbA1c on admission (%)	9.9 (8.8-11.4)	9.6 (8.8-11.1)	10.3 (8.9-11.6)	0.123

Fasting CPI on admission	1.18 (0.84-1.72)	1.08 (0.80-1.80)	1.24 (0.85-1.71)	0.486
Postprandial CPI on admission	1.70 (1.06-2.56)	1.49 (0.97-2.54)	1.83 (1.08-2.89)	0.299
Fasting CPI at discharge	1.60 (1.00-2.40)	1.17 (0.78-1.60)	2.18 (1.61-2.55)	< 0.0001
Postprandial CPI at discharge	2.71 (1.77-4.45)	2.11 (1.24-3.64)	3.32 (2.55-5.05)	< 0.0001
Diabetic neuropathy (%)	44	50	39	0.206
Diabetic retinopathy (%)	33	37	29	0.342
Diabetic nephropathy (%)	38	40	36	0.663
T-Chol (mg/dL)	179 (154-204)	172 (150-188)	186 (159-216)	0.039
TG (mg/dL)	120 (89-156)	113 (82-145)	124 (102-169)	0.083
LDL-Chol (mg/dL)	109 (89-130)	104 (89-124)	116 (90-139)	0.061
HDL -Chol (mg/dL)	42 (35-50)	43 (36-50)	40 (34-49)	0.520
AST (U/L)	20 (17-28)	19 (17-23)	21 (17-35)	0.203
ALT (U/L)	25 (16-37)	22 (15-32)	28 (18-46)	0.021
γ-GTP (U/L)	28 (19-56)	24 (17-48)	30 (20-62)	0.080
eGFR (mL/min/1.73 ㎡)	81.9 (73.1-97.9)	79.2 (71.5-92.2)	85.8 (75.2-102.5)	0.058
BNP (pg/mL)	11 (6-21)	13.6 (6.3-25.2)	8.9 (5.8-17.9)	0.010
Number of patients who received hypoglycemic agents upon admission				
Sulfonylureas (%)	21 (17)	16 (25)	5 (8)	0.008
Thiazolidinediones (%)	3 (2)	2 (3)	1 (2)	0.550
Biguanides (%)	51 (40)	23 (37)	28 (44)	0.405
α-glucosidase inhibitor (%)	11 (9)	7 (11)	4 (6)	0.330
Glinide (%)	11 (9)	6 (10)	5 (8)	0.732

DPP-4 inhibitor (%)	79 (62)	46 (73)	33 (52)	0.013
GLP-1 receptor agonist (%)	12 (9)	4 (6)	8 (13)	0.236
SGLT-2 inhibitor (%)	18 (14)	4 (6)	14 (22)	0.012
Insulin (%)	30 (24)	17 (27)	13 (20)	0.376
Number of patients who received additional hypoglycemic agents during hospitalization				
Sulfonylureas (%)	4 (3)	0(0)	4(6)	0.044
Thiazolidinediones (%)	1(1)	0(0)	1(2)	0.319
Biguanides (%)	32 (25)	12 (19)	20(31)	0.113
α-glucosidase inhibitor (%)	13 (10)	10 (16)	3 (5)	0.038
Glinide (%)	16 (13)	11(17)	5 (8)	0.101
DPP-4 inhibitor (%)	5 (4)	1 (2)	4 (6)	0.177
GLP-1 receptor agonist (%)	26 (20)	5 (8)	21 (33)	0.001
SGLT-2 inhibitor (%)	33 (26)	17 (27)	16 (25)	0.799
Insulin (%)	41 (32)	27 (43)	14 (22)	0.012

The values, except for numbers and percentages, are presented as median (interquartile range: IQR). T2D, type 2 diabetes; index-A, fasting CPI at discharge − fasting CPI on admission; BMI, body mass index; HbA1c, glycosylated hemoglobin; CPI, C-peptide index; T-Chol; total cholesterol; TG, triglyceride; LDL-Chol, low-density lipoprotein-cholesterol; HDL-Chol, high-density lipoprotein-cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; DPP-4, dipeptidyl peptide-4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose cotransporter-2.
Data were analyzed with Wilcoxon rank sum test and chi-square test.

Table 2. Multivariate logistic regression analysis for high-recovery group in the index-A.

	Model 1		Model 2		Model 3		Model 4	
Variables	Odds ratio (95%CI)	P-value	Odds ratio (95%CI)	P-value	Odds ratio (95%CI)	P-value	Odds ratio (95%CI)	P-value
Sex (male = 1, female = 0)	0.324 (0.105-1.001)	0.050	0.311 (0.098-0.987)	0.048	0.264 (0.083-0.838)	0.024	0.459 (0.144-1.460)	0.187
Age (years)	0.971 (0.941-1.003)	0.076	-	-	-	-	-	-
History of smoking (yes = 1, no = 0)	0.701 (0.234-2.098)	0.526	0.654 (0.215-1.985)	0.453	0.706 (0.237-2.105)	0.533	0.685 (0.222-2.119)	0.512
BMI on admission (kg/m^2)	-	-	1.158 (1.031-1.300)	0.014	-	-	-	-
Visceral fat area (cm^2)	-	-	-	-	1.008 (1.001-1.014)	0.020	-	-
Subcutaneous fat area (cm^2)	-	-	-	-	-	-	1.010 (1.003-1.017)	0.003

Number of patients who received hypoglycemic agents upon admission								
Sulfonylureas (%) (yes = 1, no = 0)	0.182 (0.004-0.810)	0.025	0.100 (0.020-0.500)	0.005	0.106 (0.021-0.532)	0.006	0.111 (0.022-0.557)	0.008
DPP-4 inhibitor (%) (yes = 1, no = 0)	0.443 (0.177-1.110)	0.082	0.433 (0.169-1.113)	0.082	0.428 (0.169-1.083)	0.073	0.507 (0.196-1.316)	0.163
SGLT-2 inhibitor (%) (yes = 1, no = 0)	3.478 (0.774-15.640)	0.104	5.353 (1.000-28.697)	0.05	3.660 (0.778-17.231)	0.101	5.175 (0.935-28.642)	0.060
additional hypoglycemic agents during hospitalization								
α-glucosidase inhibitor (yes = 1, no = 0)	0.224 (0.048-1.042)	0.056	0.318 (0.070-1.443)	0.138	0.270 (0.059-1.240)	0.092	0.235 (0.050-1.106)	0.067
GLP-1 receptor agonist (yes = 1, no = 0)	5.912 (1.657-21.100)	0.006	5.666 (1.551-20.701)	0.009	5.279 (1.434-19.436)	0.012	4.744 (1.275-17.657)	0.020
Insulin (%) (yes = 1, no = 0)	0.487 (0.188-1.264)	0.139	0.616 (0.232-1.640)	0.332	0.543 (0.207-1.429)	0.216	0.545 (0.204-1.452)	0.225

Odds ratios for continuous quantity are expressed as units odds ratios. 95%CI, confidence interval.

Table 3. Comparison of clinical characteristics between T2D patients with low recovery and those with high recovery of index-B and index-C

	Index-B			Index-C		
	Low-recovery group	High-recovery group	P-value	Low-recovery group	High-recovery group	P-value
Number	63	64	NA	64	63	NA
Age (years)	65 (53-76)	62 (48-71)	0.027	63 (50-74)	62 (53-72)	0.965
Male/Female	38/25	37/27	0.774	37/27	38/25	0.774
Duration of T2D (years)	10 (8-20)	8 (3-16)	0.032	10 (6-17)	10 (5-18)	0.608
Family history of diabetes (%)	73	58	0.072	64	67	0.758
History of smoking (%)	49	59	0.250	50	59	0.323
History of alcohol intake (%)	37	33	0.662	39	30	0.292
BMI at the age of 20 years (kg/m^2)	22.8 (20.3-26.3)	21.5 (20.1-25.5)	0.497	23.2 (20.3-26.4)	21.7 (20.1-24.4)	0.243
Peak BMI (kg/m^2)	29.1 (25.0-31.4)	30.1 (26.8-34.6)	0.071	30.1 (26.8-33.3)	28.7 (26.0-31.9)	0.277
BMI on admission (kg/m^2)	25.3 (21.9-27.9)	26.6 (23.6-30.1)	0.022	26.7 (23.3-30.4)	25.7 (22.7-27.5)	0.195
BMI at discharge (kg/m^2)	24.3 (21.5-27.2)	25.8 (23.1-29.8)	0.034	25.6 (22.6-29.4)	24.8 (21.9-27.2)	0.303
Changes in weight	1.2 (0.5-2.1)	2.2 (1.2-3.5)	0.673	2.2 (1.4-3.1)	2.1 (1.1-3.0)	0.396

reduction during hospitalization (kg)						
Waist circumference (cm)	92 (86-100)	98 (89-108)	0.077	96 (88-107)	93 (86-101)	0.439
Visceral fat area (cm^2)	138.4 (87.6-167.4)	165.9 (111.4-218.1)	0.022	150.3 (112.1-192.5)	143.1 (89.8-205.1)	0.655
Subcutaneous fat area (cm^2)	154.0 (101.8-211.1)	182.4 (125.9-260.4)	0.038	175.3 (109.2-225.1)	162.7 (110.4-235.5)	0.502
HbAlc on admission (%)	9.7 (8.7-11)	10.4 (8.9-11.6)	0.228	9.6 (8.5-10.7)	10.6 (9.3-12.0)	0.004
Fasting CPI on admission	1.00 (0.69-1.38)	1.36 (1.02-1.82)	0.001	1.08 (0.82-1.77)	1.27 (0.84-1.61)	0.994
Postprandial CPI on admission	1.49 (0.96-2.32)	2.05 (1.09-3.05)	0.048	1.69 (1.11-2.58)	1.70 (0.98-2.48)	0.379
Fasting CPI at discharge	1.12 (0.78-1.72)	2.12 (1.57-2.60)	< 0.0001	1.51 (0.93-2.43)	1.62 (1.23-2.40)	0.408
Postprandial CPI at discharge	1.77 (1.18-2.54)	3.89 (2.92-5.43)	< 0.0001	2.41 (1.37-3.46)	3.35 (2.20-4.97)	0.002
Diabetic neuropathy (%)	55	34	0.018	54	34	0.029
Diabetic retinopathy (%)	39	27	0.146	33	32	0.849
Diabetic nephropathy (%)	37	39	0.767	38	38	0.945
T-Chol (mg/dL)	172 (148-213)	183 (162-199)	0.392	178 (151-206)	181 (154-201)	0.682
TG (mg/dL)	105 (79-139)	135 (108-184)	0.001	118 (82-163)	120 (99-155)	0.428
LDL-Chol (mg/dL)	105 (88-133)	111 (90-130)	0.678	107 (89-130)	111 (90-134)	0.689
HDL-Chol (mg/dL)	43 (37-49)	40 (34-50)	0.286	43 (35-49)	41 (34-51)	0.716
AST (U/L)	19 (16-24)	21 (18-31)	0.049	20 (17-31)	20 (17-26)	0.915
ALT (U/L)	19 (15-35)	29 (20-42)	0.009	22 (15-42)	26 (17-35)	0.416
γ-GTP (U/L)	22 (17-43)	40 (23-62)	0.001	30 (18-56)	27 (20-60)	0.774
eGFR (mL/min/1.73m^2)	80.8 (72.8-96.4)	85.3 (73.7-99.4)	0.540	81.9 (74.5-96.7)	81.1 (71.5-99.7)	0.798

BNP (pg/mL)	13 (6-25)	9 (6-18)	0.042	12 (6-23)	10 (6-19)	0.231
Number of patients who received hypoglycemic agents upon admission						
Sulfonylureas (%)	15 (24)	6 (9)	0.029	13 (20)	8 (13)	0.248
Thiazolidinediones (%)	1 (2)	2 (3)	0.568	2 (3)	1 (2)	0.568
Biguanides (%)	27 (43)	24 (38)	0.538	30 (47)	21 (33)	0.120
α-glucosidase inhibitor (%)	8 (13)	3 (5)	0.109	7 (11)	4 (6)	0.358
Glinide (%)	10 (16)	1 (2)	0.004	8 (13)	3 (5)	0.121
DPP-4 inhibitor (%)	41 (65)	38 (59)	0.507	37 (58)	42 (67)	0.304
GLP-1 receptor agonist (%)	6 (10)	6 (9)	0.977	8 (13)	4 (6)	0.236
SGLT-2 inhibitor (%)	6 (10)	12 (19)	0.136	11 (17)	7 (11)	0.326
Insulin (%)	19 (30)	11 (17)	0.085	17 (27)	13 (21)	0.432
Number of patients who received additional hypoglycemic agents during hospitalization						
Sulfonylureas (%)	2(3)	2(3)	0.987	1 (2)	3 (5)	0.302
Thiazolidinediones (%)	1(2)	0(0)	0.235	1 (2)	0 (0)	0.319
Biguanides (%)	10 (16)	22 (34)	0.015	11 (17)	21 (33)	0.036
α-glucosidase inhibitor (%)	8 (13)	5 (8)	0.364	8 (13)	5 (8)	0.396

Glinide (%)	11 (17)	5 (8)	0.101	4 (6)	12 (19)	0.030
DPP-4 inhibitor (%)	2 (3)	3 (5)	0.661	2 (3)	3 (5)	0.635
GLP-1 receptor agonist (%)	10 (16)	16 (25)	0.203	15 (23)	11 (17)	0.404
SGLT2 inhibitor (%)	11 (17)	22 (34)	0.030	11 (17)	22 (35)	0.023
Insulin (%)	26 (41)	15 (23)	0.032	21 (33)	20 (32)	0.900

The values, except for numbers and percentages, are presented as median (interquartile range: IQR). T2D, type 2 diabetes; index-B, postprandial CPI at discharge − postprandial CPI on admission; index-C, ΔCPR (postprandial CPR − fasting CPR) at discharge − ΔCPR (postprandial CPR− fasting CPR) on admission; BMI, body mass index; HbA1c, glycosylated hemoglobin; CPI, C-peptide index; ΔCPR, postprandial C-peptide – fasting C-peptide; T-Chol, total cholesterol; TG, triglyceride; LDL-Chol, low-density lipoprotein-cholesterol; HDL-Chol, high-density lipoprotein-cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; DPP-4, dipeptidyl peptide-4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose cotransporter-2. Data were analyzed with Wilcoxon rank sum test and chi-square test.

Table 4. Multivariate logistic regression analysis for high-recovery group in the index-B.

	Model 1		Model 2		Model 3		Model 4	
Variables	Odds ratio (95%CI)	P-value	Odds ratio (95%CI)	P-value	Odds ratio (95%CI)	P-value	Odds ratio (95%CI)	P-value
Age (years)	0.997 (0.968-1.027)	0.832	-	-	-	-	-	-
BMI on admission (kg/m^2)	-	-	1.074 (0.987-1.170)	0.100	-	-	-	-
Visceral fat area (cm^2)	-	-	-	-	1.006 (1.000-1.012)	0.035	-	-
Subcutaneous fat area (cm^2)	-	-	-	-	-	-	1.003 (0.998-1.007)	0.246
TG (mg/dL)	-	-	-	-	-	-	1.003 (0.998-1.007)	0.203
γ-GTP (U/L)	1.006 (0.999-1.014)	0.113	-	-	-	-	-	-
Number of patients who received hypoglycemic agents upon admission								
Sulfonylureas (%) (yes = 1, no = 0)	0.294 (0.094-0.921)	0.036	0.298 (0.100-0.892)	0.030	0.260 (0.083-0.809)	0.020	0.297 (0.097-0.914)	0.034
Glinide (%)	0.078	0.021	0.090	0.026	0.081	0.022	0.089	0.025

(yes = 1, no = 0)	(0.009-0.682)		(0.011-0.751)		(0.001-0.694)		(0.011-0.740)	
Number of patients who received additional hypoglycemic agents during hospitalization								
Biguanides (yes = 1, no = 0)	1.688 (0.650-4.386)	0.283	1.929 (0.755-4.928)	0.170	1.792 (0.698-4.600)	0.225	1.854 (0.726-4.735)	0.197
SGLT2 inhibitor (yes = 1, no = 0)	2.425 (0.945-6.224)	0.065	2.347 (0.933-5.905)	0.070	2.225 (0.876-5.652)	0.093	2.412 (0.953-6.105)	0.063
Insulin (%) (yes = 1, no = 0)	0.553 (0.234-1.306)	0.177	0.631 (0.264-1.510)	0.301	0.634 (0.264-1.518)	0.306	0.636 (0.265-1.530)	0.312

Odds ratios for continuous quantity are expressed as units odds ratios. 95%CI, confidence interval.

Table 5. Multivariate logistic regression analysis for high-recovery group in the index-C.

	Model 1	
Variables	Odds ratio (95%CI)	P-value
HbAlc on admission (%)	1.330 (1.066-1.660)	0.009
Diabetic neuropathy (yes = 1, no = 0)	0.600 (0.274-1.314)	0.202
Biguanides (yes = 1, no = 0)	1.612 (0.645-4.030)	0.307
SGLT2 inhibitor (yes = 1, no = 0)	2.099 (0.867-5.082)	0.100

Odds ratios for continuous quantity are expressed as units odds ratios. 95%CI, confidence interval.

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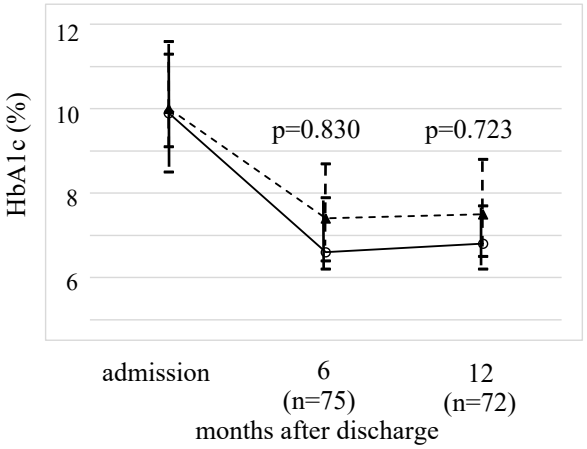

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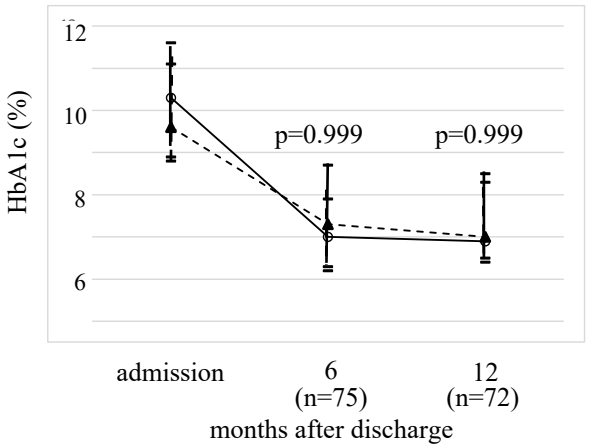

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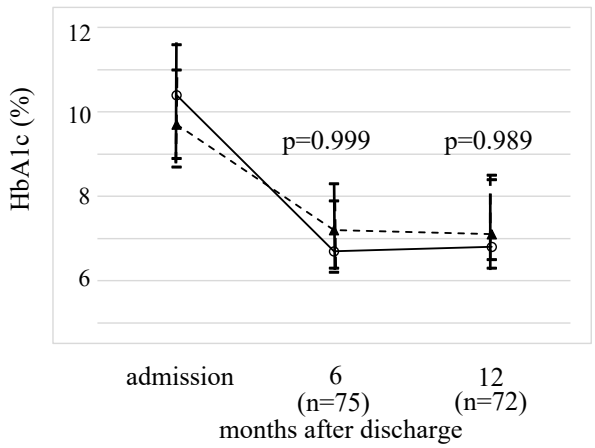

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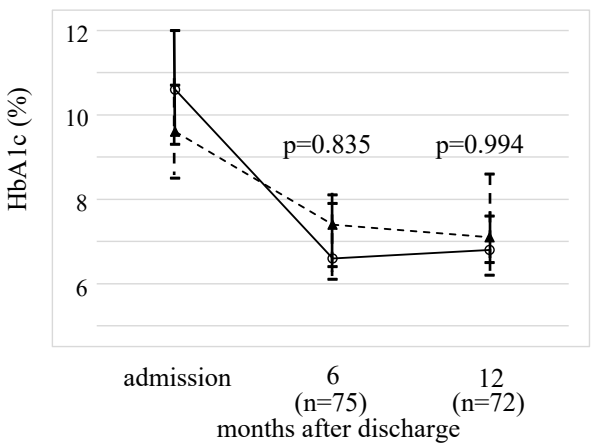
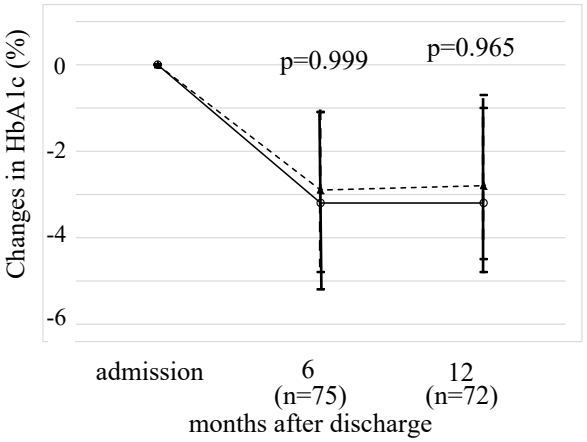
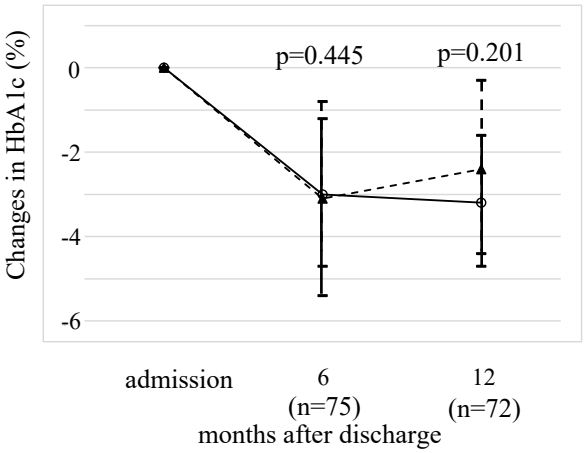


Figure 1. Enkaku

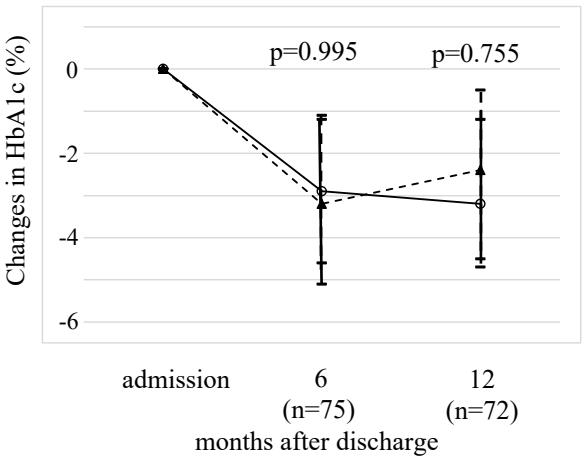
(a)



(b)



(c)



(d)

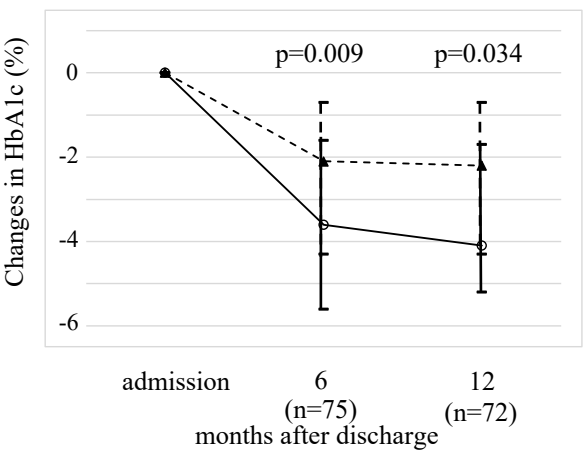


Figure 2. Enkaku

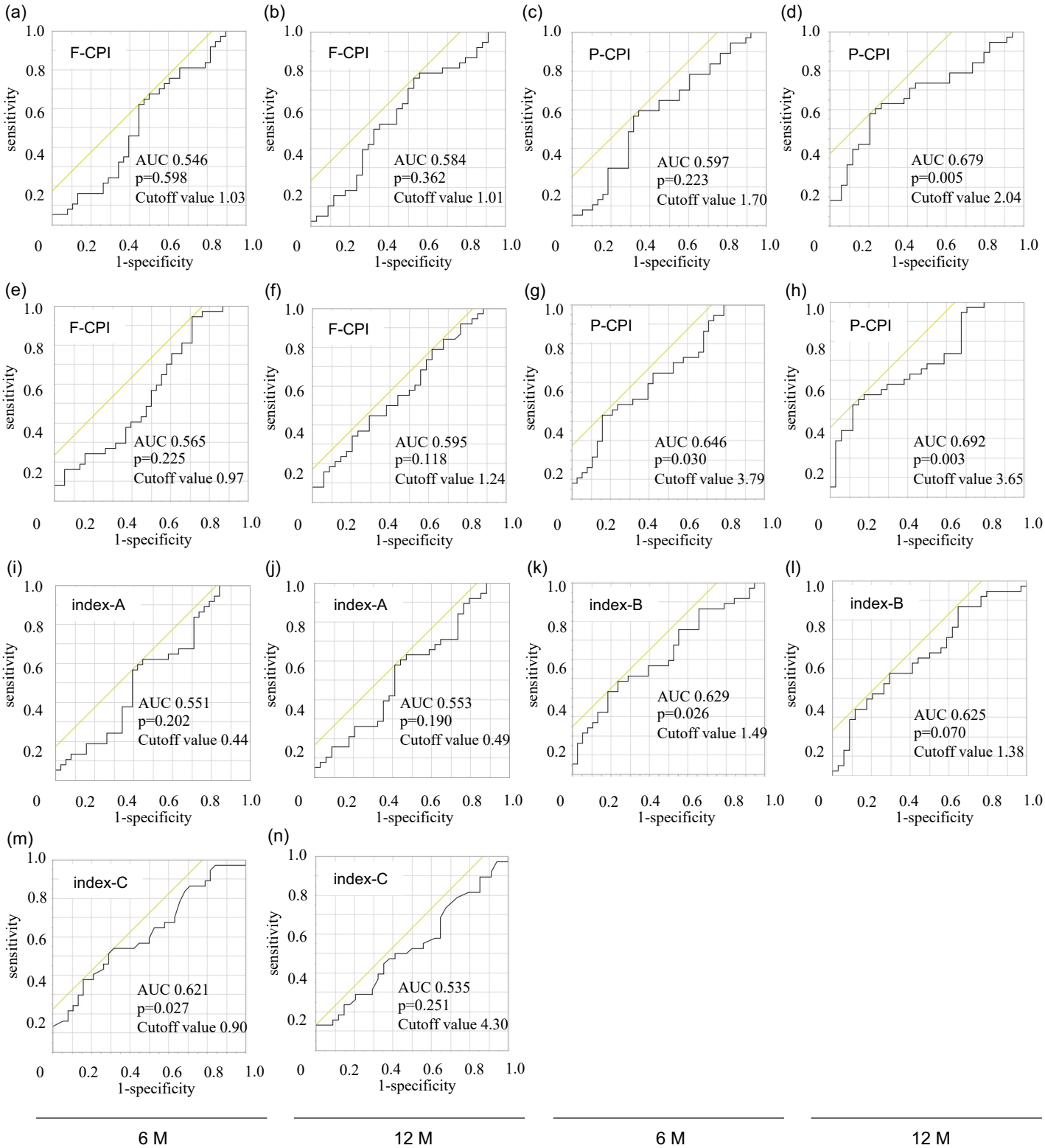


Figure 3. Enkaku

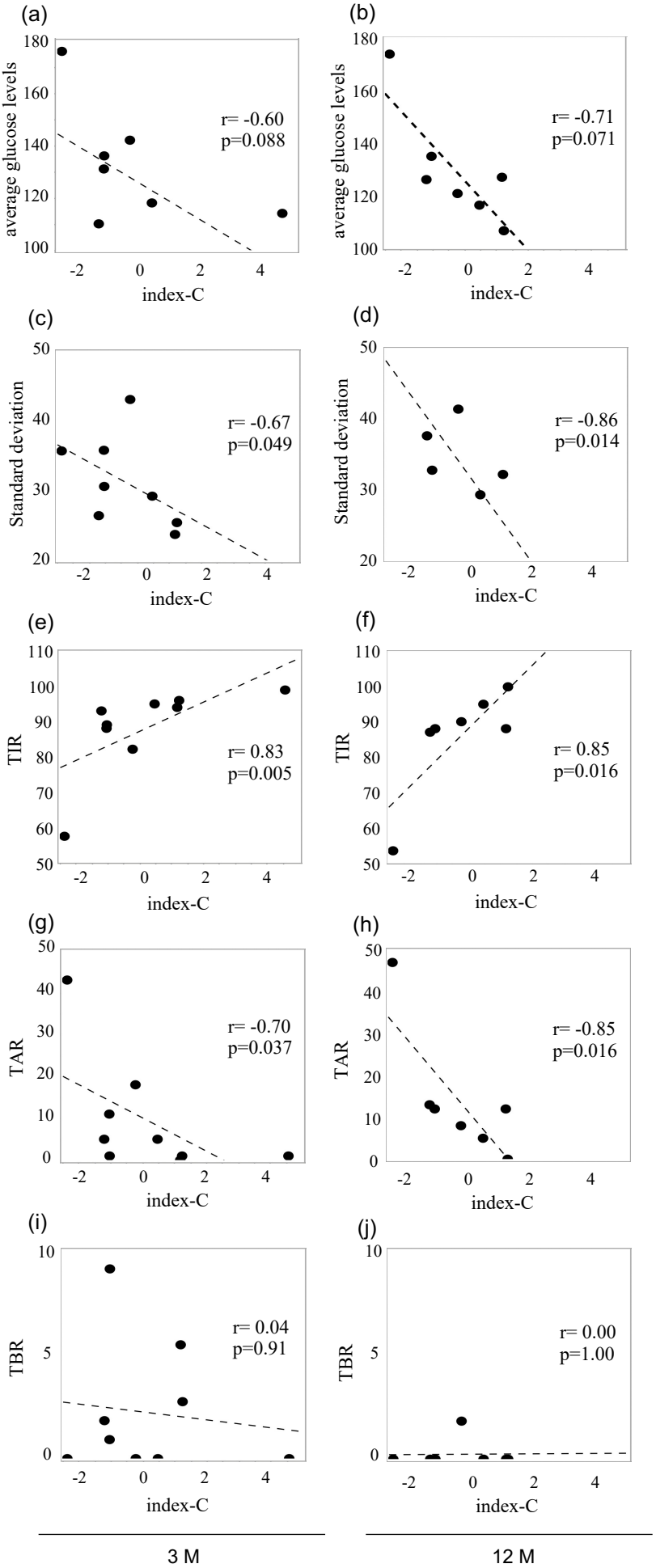


Figure 4. Enkaku

Table S1. Comparison of each index between patients with fasting plasma glucose (FPG) levels at discharge less than 126 mg/dL and those with FPG levels equal to or more than 126 mg/dL

FPG levels at discharge	< 126 mg/dL (n = 85)	≥ 126 mg/dL (n = 42)	P-value
Index-A	0.44 (0.10-0.76)	0.28 (0.03-0.79)	0.578
Index-B	1.16 (0.44-1.98)	0.99 (0.14-1.79)	0.459
Index-C	0.59 (-0.50- 2.0)	0.2 (-0.65- 1.24)	0.408

Data are shown as median (interquartile range). FPG, fasting plasma glucose
Data were analyzed with Wilcoxon rank sum test.

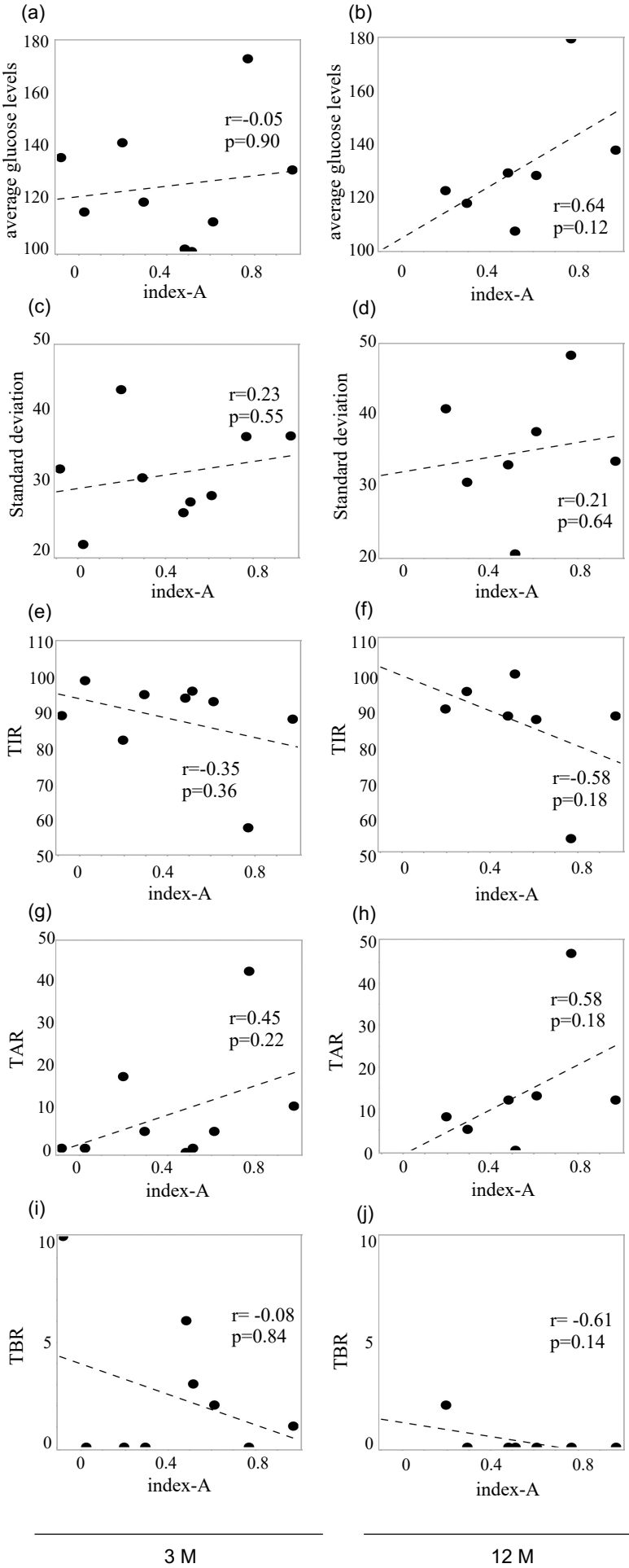


Figure S1. The correlation between index-A and glucose variability was evaluated using isCGM after discharge. (a)(b): Correlation between average glucose levels at 3 months (a) and at 12 months (b) after discharge and index-A. (c)(d): Correlation between standard deviation at 3 months (c) and at 12 months (d) after discharge and index-A. (e)(f): Correlation between TIR at 3 months (e) and at 12 months (f) after discharge and index-A. (g)(h): Correlation between TAR at 3 months (g) and at 12 months (h) after discharge and index-A. (i)(j): Correlation between TBR at 3 months (i) and at 12 months (j) after discharge and index-A. TIR, time in targeted glucose range (TIR: 70-180 mg/dL); TBR, time below targeted glucose range (TBR: < 70 mg/dL); TAR, time above targeted glucose range (TAR: > 180 mg/dL); 3 M, 3 months after discharge; 12 M, 12 months after discharge Data were analyzed with Spearman's correlation coefficient .

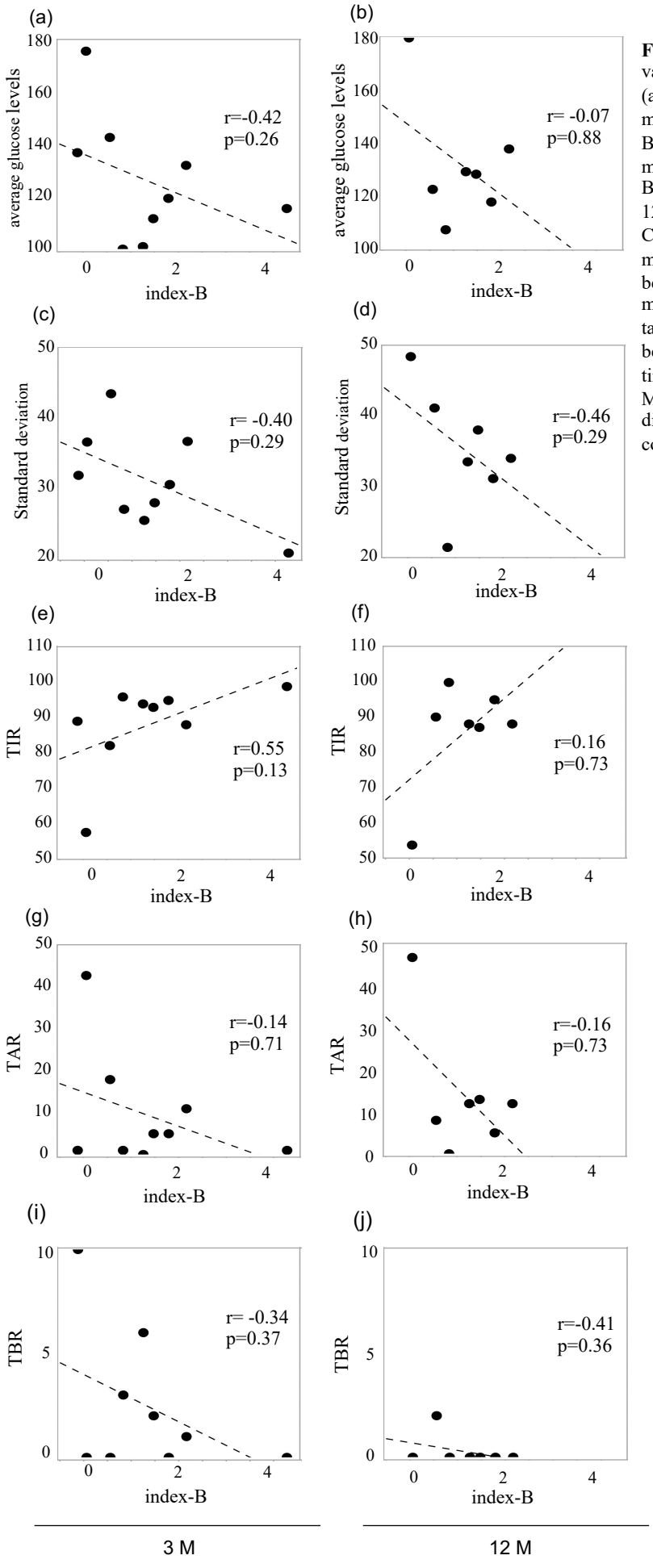


Figure S2. The correlation between index-B and glucose variability was evaluated using isCGM after discharge. (a)(b): Correlation between average glucose levels at 3 months (a) and at 12 months (b) after discharge and index-B. (c)(d): Correlation between standard deviation at 3 months (c) and at 12 months (d) after discharge and index-B. (e)(f): Correlation between TIR at 3 months (e) and at 12 months (f) after discharge and index-B. (g)(h): Correlation between TAR at 3 months (g) and at 12 months (h) after discharge and index-B. (i)(j): Correlation between TBR at 3 months (i) and at 12 months (j) after discharge and index-B. TIR, time in targeted glucose range (TIR: 70-180 mg/dL); TBR, time below targeted glucose range (TBR: < 70 mg/dL); TAR, time above targeted glucose range (TAR: > 180 mg/dL); 3 M, 3 months after discharge; 12 M, 12 months after discharge. Data were analyzed with Spearman's correlation coefficient .