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ORIGINAL ARTICLE

Usefulness of subclassification of adult diabetes mellitus among inpatients in Japan

Kohei Saito[1,2,3], Tatsuhide Inoue[1], Hiroyuki Ariyasu[1], Toshio Shimada[3], Hiroshi Itoh[2], Issei Tanaka[1], Chikashi Terao[3,4,5]*

[1]Center for Diabetes, Endocrinology and Metabolism, Shizuoka General Hospital, Shizuoka, Japan, [2]Department of Endocrinology, Metabolism and Nephrology, Keio University School of Medicine, Tokyo, Japan, [3]Clinical Research Center, Shizuoka General Hospital, Shizuoka, Japan, [4]Department of Applied Genetics, School of Pharmaceutical Sciences, University of Shizuoka, Shizuoka, Japan, and [5]Laboratory for Statistical and Translational Genetics, RIKEN Center for Integrative Medical Sciences, Kanagawa, Japan

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***Correspondence**
Chikashi Terao
Tel.: +81-54-247-6111
Fax: +81-54-247-6140
E-mail address:
chikashi.terao@riken.jp

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ABSTRACT

Aims/Introduction: We aimed to replicate a new diabetes subclassification based on objective clinical information at admission in a diabetes educational inpatient program. We also assessed the educational outcomes for each cluster.

Methods: We included diabetes patients who participated in the educational inpatient program during 2009–2020 and had sufficient clinical information for the cluster analysis. We applied a data-driven clustering method proposed in a previous study and further evaluated the clinical characteristics of each cluster. We investigated the association between the clusters and changes in hemoglobin A1c level from the start of the education program. We also assessed the risk of re-admission for the educational program.

Results: We divided a total of 651 patients into five clusters. Their clinical characteristics followed the same pattern as in previous studies. The intercluster ranking of the cluster center coordinates showed strong correlation coefficients with those of the previous studies (mean $\rho = 0.88$). Patients classified as severe insulin-resistant diabetes (cluster 3) showed a more pronounced progression of renal dysfunction than patients classified as the other clusters. The patients classified as severe insulin-deficient diabetes (cluster 2) had the highest rate of reduction in hemoglobin A1c level from the start of the program ($P < 0.01$) and a tendency toward a lower risk of re-admission for the education program (hazard ratio 0.47, $P = 0.09$).

Conclusion: We successfully replicated the diabetes subclassification using objective clinical information at admission for the education program. In addition, we showed that severe insulin-deficient diabetes patients tended to have better educational outcomes than patients classified as the other clusters.

INTRODUCTION

Diabetes, one of the most challenging global health problems, is a leading cause of microvascular and macrovascular diseases[1]. Diabetes is classified into four major categories according to the conventional classification[2], of which type 2 diabetes accounts for the majority, nearly 90%[3]. However, as diabetes is a highly heterogeneous disease involving genetic and environmental factors[4], there is a wide variation in treatment response and complication progression among patients with type 2 diabetes[5]. Therefore, a new and more sophisticated classification system for diabetes is required to achieve precision medicine for diabetes.

Recently, Ahlqvist *et al.*[6] developed a novel subclassification method to classify diabetes patients into five clusters. They used a data-driven clustering method with six variables (i.e., age at diagnosis, body mass index [BMI], hemoglobin A1c [HbA1c], homeostatic model assessment-2 β-cell function [HOMA2-B], homeostatic model assessment-2 insulin resistance [HOMA2-IR] and glutamic acid decarboxylase antibodies [GADA]). In the subclassification, patients with positive GADA were assigned to severe autoimmune diabetes (SAID), whereas the other GADA-negative patients were classified into four categories: (i) severe insulin-deficient diabetes (SIDD); (ii) severe insulin-resistant diabetes (SIRD); (iii) mild obesity-related diabetes (MOD); and (iv) mild age-related diabetes (MARD). Furthermore, this subclassification was replicated in several studies with large prospective cohorts[7–10]. However, there are several

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limitations to this clustering method. First, the applicability of clustering methods in the absence of data at the onset of diabetes has not yet been adequately explored. In particular, in the real world, it is often the case that patients do not undergo a comprehensive examination for the assessment of diabetes at their first visit. Second, previous studies have mainly applied subclassification to outpatients, with no previous studies focusing on inpatients. Finally, the relevance of this subclassification to clinical outcomes, especially educational outcomes, which are key to diabetes care, is still unclear[7,8].

Diabetes specialty facilities in Japan offer an educational inpatient program for patients who require intensive intervention to enhance their self-reliance in diabetes care. The program aims to improve glycemic control and long-term prognosis based on a thorough understanding of the individual's level of self-reliance in diabetes care, the progression of complications and pathophysiological characteristics. However, key factors that predict the effectiveness of educational programs have not yet been determined[11].

The present study aimed to evaluate the usefulness of the clustering method using objective clinical information obtained through the educational program. We also evaluated the relationship between the clusters and educational outcomes.

MATERIALS AND METHODS

Design and setting

We carried out a single-center, observational study of patients who visited the Center for Diabetes, Endocrinology and Metabolism at Shizuoka Prefectural Shizuoka General Hospital and participated in the educational admission program. The attending physician specializing in diabetes determines the program's participation for patients who require an educational intervention (e.g., when treatment goals are not met at regular visits, when complications arise, or when life or care transitions occur). The program requires hospitalization for a total of 2 weeks. The participants receive guidance from specialist healthcare professionals (doctors, nurses, dieticians, occupational therapists and dental hygienists) on diet, exercise, insulin injections and self-monitoring of blood glucose levels. They are also assessed for the progression of diabetes-related complications and reviewed on their treatments.

Study participants

The study included 1,180 consecutive patients who underwent the educational admission program at Shizuoka General Hospital between January 2009 and December 2020. Of these, we included 714 patients with type 1 or type 2 diabetes defined by discharge diagnosis codes (International Classification of Disease 10the revision: E10 and E11) with complete data available at baseline for the six model variables of the cluster analysis (HbA1c, age, BMI, HOMA2-B, HOMA2-IR and GADA). The other types of diabetes, such as gestational diabetes, maturity-onset diabetes of the young, pancreatic diabetes and steroid-induced hyperglycemia, were excluded[8]. In addition, to avoid misclassification of patients with steroid-induced hyperglycemia and pancreatic diabetes, we further excluded 43 patients with a history of oral and injectable steroid administration within 3 months before the admission and/or with a pancreatic cancer diagnosis code (C25). Furthermore, 20 patients were excluded from the current analysis, because the mean value of any model variables was more than five standard deviations (separately calculated for men and women).

Clinical information

We collected the baseline characteristics from electronic medical records at initial participation in the program. If data were missing during the hospitalization, we collected them over a period extending to 1 month before the admission and 1 month after the discharge. In addition, fasting blood glucose (FBG) and C-peptide immunoreactivity (CPR) were limited to those measured in the morning after overnight fasting under hospitalization). We collected primary clinical information and biochemical data, including variables for clustering, as follows: age at the admission, sex, BMI, biochemical information, drug information, HbA1c, FBG, CPR, HOMA2-B, HOMA2-IR, aspartate aminotransferase, alanine aminotransferase, γ- glutamyl transpeptidase, estimated glomerular filtration rate (eGFR), creatinine, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, triglycerides, 24-h urine microalbuminuria and GADA. In the absence of the data of the 24-h urine microalbuminuria, we estimated urinary albumin excretion for 1 day using the albumin/creatinine ratio. GADA was defined to be positive if there was a record of exceeding the cut-off value (see below) at any point in the history of our visit. In addition, we collected the HbA1c levels, measured regularly during the outpatient visit. The electronic medical records of Shizuoka General Hospital (Shizuoka, Japan) were a generally available electronic medical record system in Japan (NEWTON until December 2015, Software Service, Osaka, and HOPE/EGMAIN-GX since January 2016, Fujitsu, Tokyo).

Measurements

CPR was measured by electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany). GADA was measured using a commercially available radioimmunoassay kit (Cosmic Ltd, Tokyo, Japan) until 17 December 2015 and using a commercially available enzyme-linked immunosorbent assay kit (RSR Ltd., Cardiff, UK) from 18 December 2015. The cut-off value for GADA measured using a radioimmunoassay kit and GADA measured using an enzyme-linked immunosorbent assay kit was 0.5 and 5.0 U/mL[12], respectively. HOMA2-B and HOMA2-IR were estimated from FBG and CPR using the Homeostasis Model Assessment calculator (University of Oxford, Oxford, UK)[13]. HbA1c level was measured using the enzymatic assay kit (Arkray Ltd, Tokyo, Japan). The eGFR (mL/min/1.73 m^2) was calculated as $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ (if female)[14].

k-means clustering

Following the previous study[6], we assigned GADA-positive patients to the SAID cluster, whereas the other GADA-negative patients were subjected to *k*-means clustering using the remaining five variables (e.g., age at admission, BMI, HbA1c, HOMA2-B and HOMA2-IR). The *k*-means clustering was carried out separately for men and women using standardized values of the five variables with a mean of 0 and standard deviation of 1[6]. The stats package (k = 4, nstart = 25, iter.max = 100) of R version 3.6.3 (The R Foundation for Statistical Computing, Vienna, Austria) was used[15]. We assigned four names (SIDD, SIRD, MOD and MARD) to the four clusters based on their clinical characteristics. To verify the consistency of the clusters with the same names between the results of the present study and those of previous large cohort studies[6,7], we assessed the intercluster ranking of cluster center coordinate and compared the rankings using Spearman's correlation coefficient.

Evaluation of educational outcomes

We evaluated alterations of the HbA1c levels after the admission in each cluster using a generalized additive model (n = 651) to assess the outcome of the educational program.

For those with follow-up data available for >180 days (n = 475), we evaluated the association between HbA1c reduction and clusters using multivariable linear regression models, adjusting for age, BMI, eGFR, hemoglobin, HOMA2-IR and HOMA2-B. We defined the HbA1c reduction as the difference between the baseline HbA1c level and the HbA1c level at the first outpatient visit >180 days after the educational hospitalization.

We used the Cox regression model to evaluate the risk of readmission for the same educational program among clusters, adjusting for age, sex, HbA1c and eGFR. We excluded SAID patients, mainly including type 1 diabetes, from the comparative analysis. We defined the follow-up period as the period from the date of initial admission to the last date of regular visit. Interruption of regular visits for more than a year was regarded as the termination of visiting the hospital.

Statistical analysis

Intercluster comparisons of the baseline characteristics were carried out using the Mann–Whitney *U*-test for continuous variables, and the χ^2-test for categorical variables. Two-tailed probability values of <0.05 were considered statistically significant. All statistical analyses were carried out using R version 3.6.3 (The R Foundation for Statistical Computing)[15].

RESULTS

Baseline characteristics of the participants

The present study included a total of 651 patients (Table 1). The proportion of women was 36%, and the median age at admission was 63 years (interquartile range 51–72 years). The conventional classification showed 32 of 651 (4.9%) for type 1 diabetes, 546 of 651 (83.9%) for type 2 diabetes and 73 of 651 (11.2%) for latent autoimmune diabetes in adults (Table S1), reflecting the enrichment of challenging cases with poor glycemic control, especially GADA-positive cases, referred to the diabetes center.

Table 1 | Participants' characteristics

Item	Values
No. participants	651
Sex, female (%)	233 (35.8)
Age at admission (years)	63.0 [51.0–72.0]
BMI (kg/m^2)	24.3 [21.4–27.4]
HbA1c (%)	10.5 [9.1–12.4]
FBG (mg/dL)	160 [131–204]
CPR (pg/mL)	1.7 [1.0–2.4]
HOMA2-B (%)	37.2 [23.1–57.1]
HOMA2-IR	1.5 [0.9–2.2]
Hemoglobin (g/dL)	14.0 [12.8–15.2]
MCV (fL)	89.0 [86.0–92.0]
AST (IU/L)	20.0 [16.0–29.0]
ALT (IU/L)	21.0 [15.0–34.0]
γGTP (IU/L)	29.0 [19.0–54.0]
eGFR (mL/min/1.73 m^2)	81.0 [60.5–99.0]
Creatinine (mg/dL)	0.7 [0.6–0.9]
HDL-c (mg/dL)	45.0 [39.0–57.0]
LDL-c (mg/dL)	114 [90.0–138]
Triglyceride (mg/dL)	124 [87.0–180]
Urinary albumin excretion (g/day)	11.8 [5.6–47.9]
eGFR <60 mL/min/1.73 m^2 (%)	153 (24.1)
eGFR < 45 mL/min/1.73m^2 (%)	68 (10.7)
Treatment	
Metformin (%)	216 (33.2)
Thiazolidinediones (%)	8 (1.2)
Sulfonylurea (%)	46 (7.1)
Glinides (%)	119 (18.3)
Alpha-glucosidase inhibitors (%)	98 (15.1)
SGLT2 inhibitors (%)	85 (13.1)
DPP4 inhibitors (%)	304 (46.7)
GLP-1 receptor agonists (%)	135 (20.7)
Insulin injections (%)	528 (81.1)
Statins (%)	232 (35.6)

Data presented as n (%) or n [interquartile range]. γGTP, γ-glutamyl transpeptidase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CPR, C-peptide immunoreactivity; DPP4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol, MCV; mean cell volume; SGLT2, sodium–glucose co-transporter 2.

Subclassification of participants using data-driven clustering

We carried out the data-driven clustering to classify the patients into the five clusters using their clinical information at admission (Figure 1). Then, we assigned the clustering labels to the corresponding clusters based on the clinical characteristics

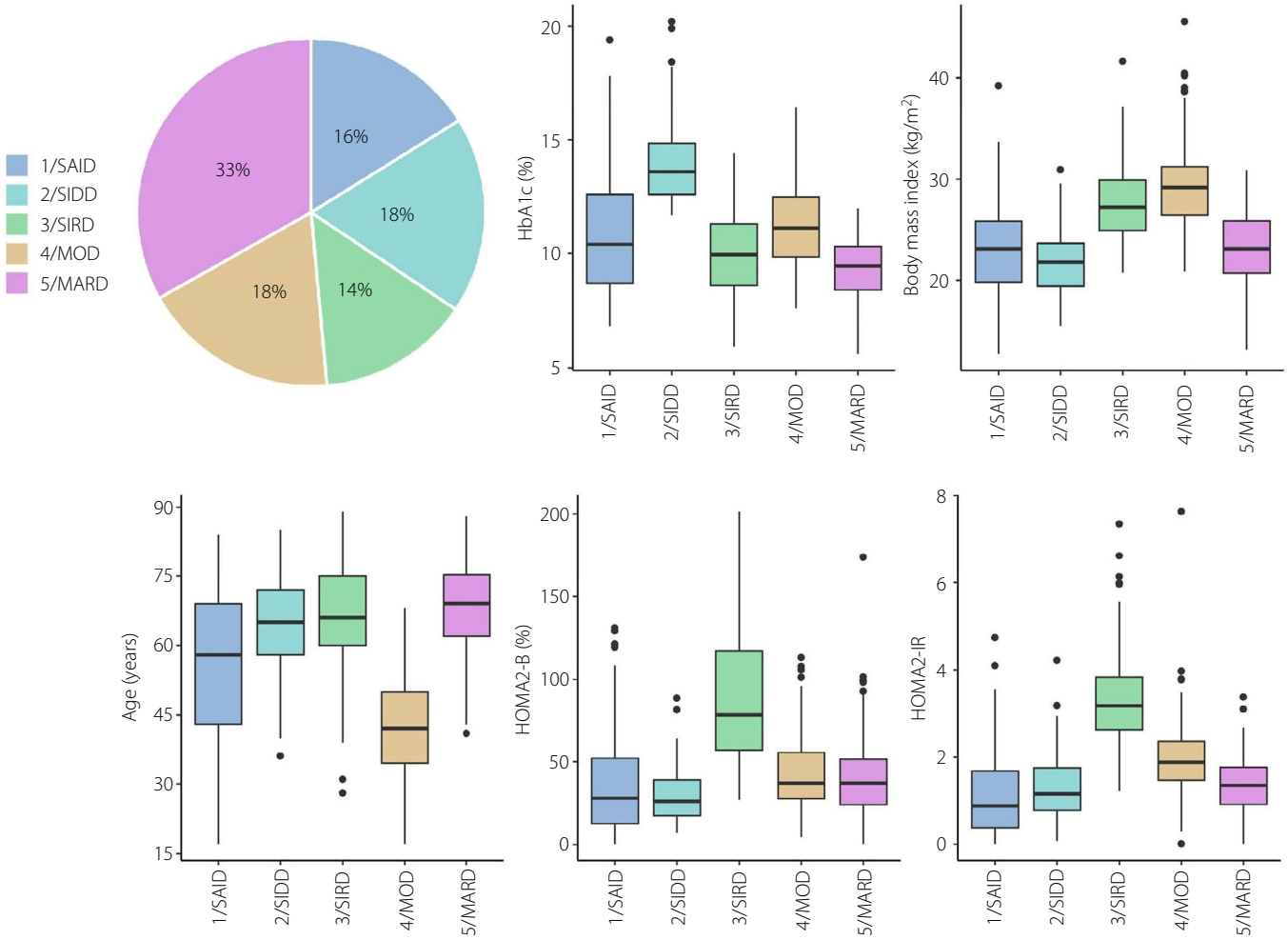

Figure 1 | Distributions of the five clusters and clinical characteristics of each cluster (n = 651). The cluster analysis was carried out separately for men and women, and then combined. HOMA2-IR and HOMA2-B are calculated by C-peptide immunoreactivity and fasting blood glucose[13]. The six clinical parameters (age, body mass index [BMI], hemoglobin A1c [HbA1c], homeostatic model assessment 2 estimates of insulin resistance [HOMA2-IR], homeostatic model assessment 2 estimates of β-cell function[HOMA2-B] and glutamic acid decarboxylase antibodies [GADA]) are used in the cluster analysis. All the GADA-positive patients are assigned to the severe autoimmune diabetes (SAID; cluster 1). The colors assigned to each cluster are consistent across the box-and-whisker plots. MARD, mild age-related diabetes; MOD, mild obesity-related diabetes; SIDD, severe insulin-deficient diabetes; SIRD, severe insulin-resistant diabetes.

reported in the previous study[6]. The clustering results were very similar between men and women (Figure S1A and B). Overall, we found that the distribution of the participants into clusters was comparable to the distribution of each cluster in the previous studies[6–9] (Figure 1; Figure S2). Meanwhile, there was a slightly high proportion of SAID patients in the current study in concordance with the enrichment of GADA- positive cases discussed above (Figure 1).

Furthermore, we found that each cluster had quite similar patterns of clinical features to the previous study[6]. The SAID patients (cluster 1), characterized by positive GADA, showed slightly younger age and lower HOMA2-B. The SIDD patients (cluster 2), characterized by severely impaired insulin secretion, showed higher HbA1c and lower HOMA2-B. The SIRD patients (cluster 3), characterized by severe insulin resistance, showed higher BMI and higher HOMA2-IR, and a significantly higher rate of renal dysfunction (Table S2). The MOD patients (cluster 4), characterized by severe obesity with mild insulin resistance, showed younger age, higher BMI and higher HOMA2-IR. The MARD patients (cluster 5) were characterized by older age and mild glucose intolerance.

We further used center coordinates to show the consistency of the clustering results with the previous results of center coordinates[6,7] (Table S3). The Spearman's correlation coefficients of the cluster center coordinates between the present study and the previous studies[6,7] were almost >0.8 (mean ρ = 0.88;

Table S4). Also, the relative ranking relationships in the present study were shown to be quite similar to those of the previous studies (Figure S3). These results showed that the clustering method successfully classified the diabetes patients in the current study into five clusters with similar patterns of clinical characteristics, even though we mainly utilized clinical information at the time of educational admission instead of at the onset of diabetes.

Evaluation of the educational impact in each cluster

We then assessed the effectiveness of the education to find novel clinical implications of this subclassification. To evaluate the educational outcomes among the clusters, we assessed the longitudinal changes of the HbA1c level in each cluster (n = 651, overall median follow up: 2.0 years [interquartile range 0.4–4.2 years]). The results showed a common trend among all clusters: the HbA1c level began to decline immediately after the educational program and reached a plateau after approximately 3–6 months (Figure 2). These results show substantial and long-lasting benefits of the educational program across all of the clusters. Meanwhile, the SIDD patients (cluster 2), with the highest HbA1c levels at baseline of all the clusters, showed the most significant decline in the HbA1c level (β = –3.27; 95% confidence interval –4.05 to –2.49; $P < 1.0 \times 10^{-10}$; Figure 2; Table S5). To further investigate the possible advantage of the SIDD patients, the Cox regression models were used to compare the risk of re-admission between the SIDD patients and patients in other clusters (SIRD, MOD and MARD) after adjusting for age, sex, HbA1c and eGFR. As a result, we observed a trend toward a lower risk of re-admission (the repetitive requirement for the educational program) in the SIDD patients (hazard ratio 0.32, 95% confidence interval 0.09–1.15, P = 0.08; Figure 3; Figure S4; Table S6). These results suggest that the educational effect for the SIDD patients tends to be higher than for patients in other clusters, and that this subclassification might help select patients who should receive intensive educational interventions.

DISCUSSION

We have retrospectively replicated the diabetes subclassification method proposed by Ahlqvist *et al.*[6] The present study had three novel aspects. First, while other previous studies mainly

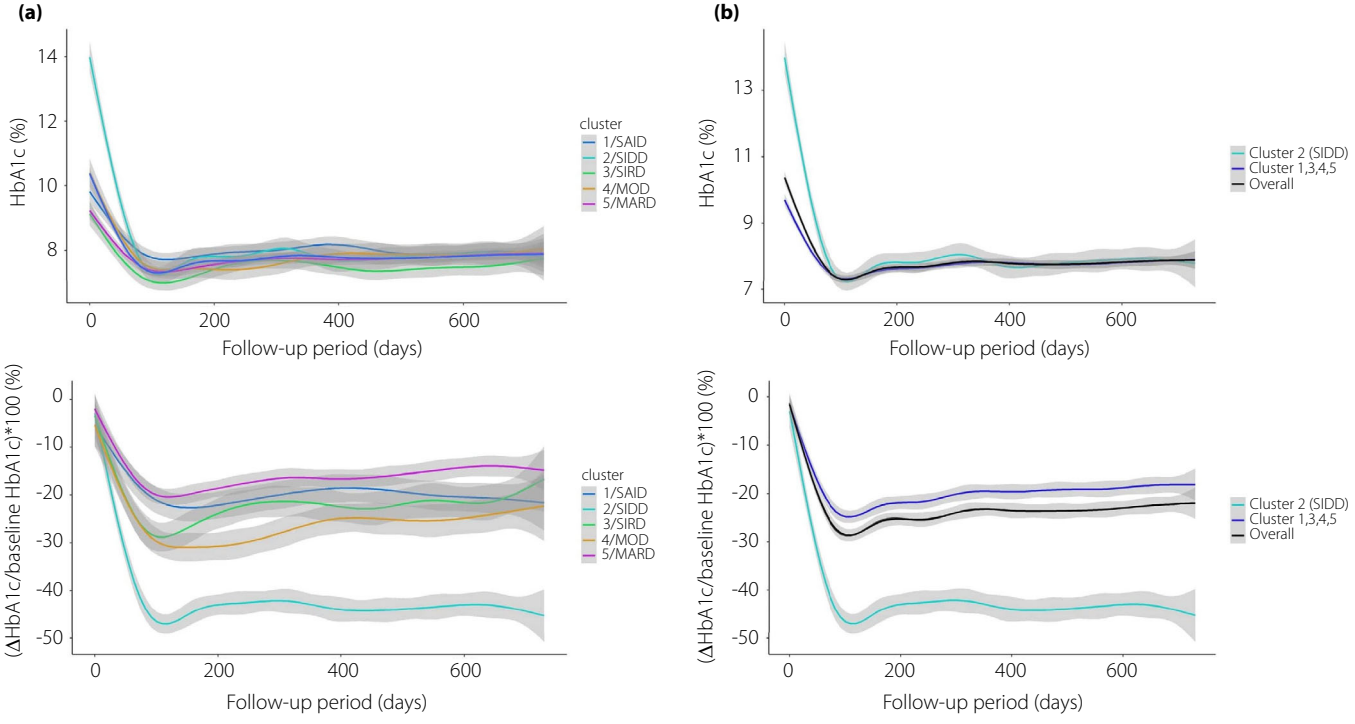

Figure 2 | Hemoglobin A1c (HbA1c) trend after initiation of the educational program. The change in HbA1c levels after the educational program are compared (a) among clusters and (b) between severe insulin-deficient diabetes (SIDD) and the other clusters. The *x*-axis represents the follow-up period. The *y*-axis represents the HbA1c value (upper panel) and the average rate of change in HbA1c (lower panel), calculated by dividing the HbA1c value by that at baseline. This curvilinear graph uses a generalized additive model, where the gray zone is defined as a 95% confidence level interval (n = 651). HOMA2-B, homeostatic model assessment 2 estimates of β-cell function; HOMA2-IR, homeostatic model assessment 2 estimates of insulin resistance; MARD, mild age-related diabetes; MOD, mild obesity-related diabetes; SAID, severe autoimmune diabetes; SIRD, severe insulin-resistant diabetes.

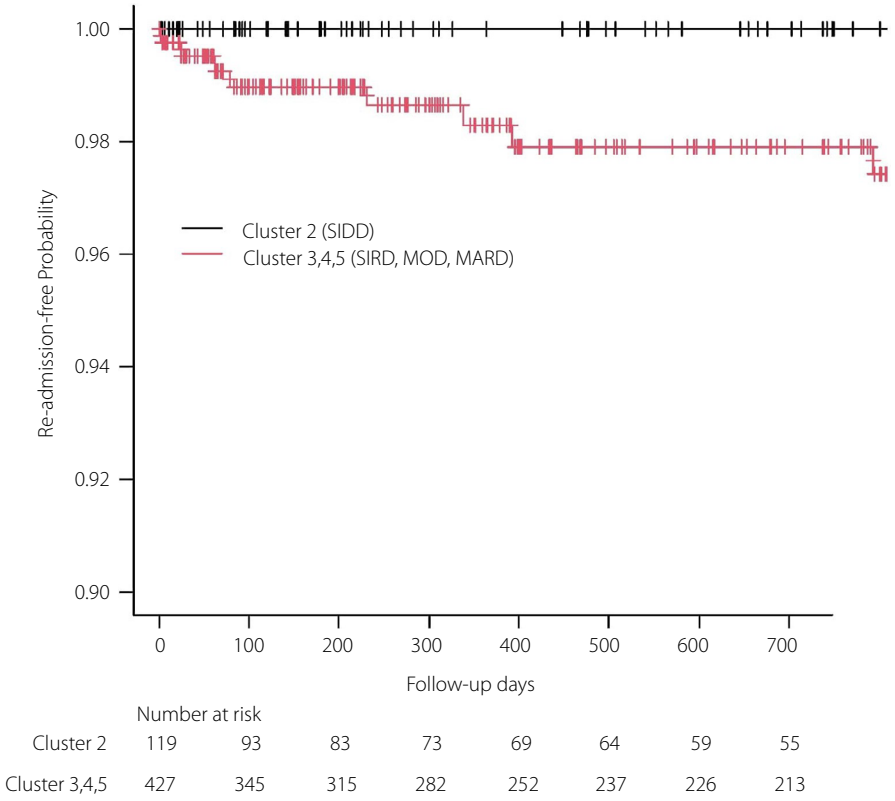

Figure 3 | Differences of re-admission risk for the educational program among the clusters. The Kaplan–Meier curve was used to show the probability of no second admission for the same program from the end of the first educational program. We compared cluster 2 with the other clusters (both mainly including type 2 diabetes). We adjusted for age at the first admission, sex, hemoglobin A1c and estimated glomerular filtration rate using the Cox regression model ($P = 0.08$). As the number of censored cases increases after 2 years, the figure is presented for 2 years (shown for the entire period in Figure S4). MARD, mild age-related diabetes; MOD, mild obesity-related diabetes; SIDD, severe insulin-deficient diabetes; SIRD, severe insulin-resistant diabetes.

used data at onset, this study used data irrespective of onset, taking into account real-world clinical practice where data at onset is often insufficient. The results of the present study are a significant step forward in introducing this subclass classification into clinical practice. Especially in Japan, patients often do not have sufficient information. Clinicians would like to apply it to hospitalized patients for whom sufficient information is not available at the first visit. Second, this is the first time the subclassification of patients requiring educational admission with poor diabetic control has been applied, which is particularly important in Japan, where many patients are required to be admitted for diabetes education. Finally, although the significance of the clinical results is not yet clear, it is a notable novelty that the study showed that SIDD patients in clusters were most likely to benefit from the education program.

We showed that the clustering method is robust using the values of the cluster center coordinates, as well as their patterns of distribution and clinical characteristics. These results showed the adaptability of the subclassification across races, which is consistent with the results of the previous studies including Asian populations[6–10]. Furthermore, the SIRD patients had a significantly higher rate of renal dysfunction at baseline. Zaharia *et al.*[8] found that patients in the SIRD patients group had lower eGFR and higher cystatin-C levels at both baselines and after 5 years, even with better glycemic and lipid control. Given the strong association between insulin resistance and impaired renal function[16], it seems to be plausible that SIRD patients are prone to diabetic nephropathy. Furthermore, in the present study, the absolute values of BMI, HOMA2-B and HOMA2-IR were lower than in European studies[6–8]. These results are consistent with previous reports involving Asian participants[9,10] and might reflect racial differences in the pathogenesis of diabetes.

There is also some debate regarding the clinical parameters used for subclassification. In the past, some reports reported the possible use of C-peptide or high-density lipoprotein cholesterol instead of HOMA2-B or HOMA2-IR[17], and another study concluded that simple clinical features were more helpful in predicting the risk of diabetic complications[18]. Hence, further research is required to determine what clinical parameters should be used for a more practical subclassification.

This is the first study to apply the subclassification to inpatients with diabetes using objective clinical information available at admission. In general, it is difficult to know the point of the onset precisely due to the lack of subjective symptoms. In addition, the diagnostic history information provided in the interview or questionnaire is not always accurate.

To the best of our knowledge, we first evaluated the difference in outcomes of the educational admission program among clusters. Several studies have reported that the intervention of a team of diabetes experts in hospitalized patients has reduced re-admissions after discharge[19–21]. In the current study, we found that the reduction rate of HbA1c after the educational program was more pronounced in SIDD. Furthermore, the risk of re-admission for the educational program tended to be lower in SIDD than in the other clusters. These results show that the educational effect might be remarkable and long-lasting for diabetes patients in SIDD. Possible explanations for the trend toward greater educational effectiveness in patients with SIDD were as follows. SIDD patients had severe insulin deficiency and the highest HbA1c of all clusters, whereas this group had relatively low insulin resistance and could be considered to be sensitive to insulin therapy. In addition, although the educational content of the educational admission for type 2 diabetes was basically the same, insulin users are given additional instruction on the appropriate use of insulin. Therefore, it was possible that appropriate educational guidance or introduction on insulin use might affect educational outcomes, particularly for SIDD patients, almost all of whom (96%) were on insulin therapy. However, the number of cases and the follow-up period in the present study might be insufficient to detect the significant differences in the long-term outcomes among the clusters. Thus, future studies will need to observe the educational effects from larger cohorts over a more extended period.

Although the current single-center observational study provided us with homogeneous data at the admission for the educational program, there were several limitations. First, we cannot ignore the effect of selection bias. Although we took all patients who participated in the education program into account, subjective factors of the doctor might confound the determination of the entry to the program. Therefore, it is favorable to verify the results in multicenter studies. Second, there is a possibility that we overlooked the re-admission of the patients for a similar educational program at other facilities not captured by the system of our center. Third, the present study lacked enough follow-up data to assess the risk of developing microvascular and macrovascular complications, major targets of interest in diabetes care.

In conclusion, we successfully replicated the novel diabetes subclassification based on the clinical information at the admission of the educational program. In addition to the distribution of each cluster, we observed strong similarities in clinical characteristics with previous reports. Among all the clusters, SIDD patients tended to benefit the most from the educational program, implying the clinical usefulness of the subclassification. We need a multicentered prospective cohort study further to explore the utilization and application of the novel subclassification.

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DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: This study was carried out in accordance with the guidelines for clinical research by Japan's Ministry of Health, Labor and Welfare, and the ethical standards outlined in the 1964 Declaration of Helsinki and its subsequent amendments. This study was approved by the Ethics Committee of Shizuoka Prefectural General Hospital.

Informed consent: Informed consent was obtained through an opt-out methodology.

Approval date of registry and the registration no. of the study/-trial: N/A.

Animal studies: N/A.

REFERENCES

1. Ogurtsova K, da Rocha Fernandes JD, Huang Y, *et al*. IDF Diabetes Atlas: global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res Clin Pract* 2017; 128: 40–50.
2. Classification and diagnosis of diabetes. *Diabetes Care* 2017; 40(Suppl 1): S11–S24.
3. Chatterjee S, Davies MJ. Accurate diagnosis of diabetes mellitus and new paradigms of classification. *Nat Rev Endocrinol* 2018; 14: 386–387.
4. Tuomi T, Santoro N, Caprio S, *et al*. The many faces of diabetes: a disease with increasing heterogeneity. *Lancet* 2014; 383: 1084–1094.
5. Karalliedde J, Gnudi L. Diabetes mellitus, a complex and heterogeneous disease, and the role of insulin resistance as a determinant of diabetic kidney disease. *Nephrol Dial Transplant* 2016; 31: 206–213.
6. Ahlqvist E, Storm P, Käräjämäki A, *et al*. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol* 2018; 6: 361–369.
7. Dennis JM, Shields BM, Henley WE, *et al*. Disease progression and treatment response in data-driven subgroups of type 2 diabetes compared with models based on simple clinical features: an analysis using clinical trial data. *Lancet Diabetes Endocrinol* 2019; 7: 442–451.
8. Zaharia OP, Strassburger K, Strom A, *et al*. Risk of diabetes-associated diseases in subgroups of patients with recent-

onset diabetes: a 5-year follow-up study. *Lancet Diabetes Endocrinol* 2019; 7: 684–694.
9. Li X, Yang S, Cao C, *et al*. Validation of the Swedish diabetes re-grouping scheme in adult-onset diabetes in China. *J Cli Endocrinol Metab* 2020; 105: e3519–e3528.
10. Tanabe H, Saito H, Kudo A, *et al*. Factors associated with risk of diabetic complications in novel cluster-based diabetes subgroups: a Japanese retrospective cohort study. *J Clin Med* 2020; 9: 2083.
11. Sonoda R, Tanaka K, Kikuchi T, *et al*. C-Peptide level in fasting plasma and pooled urine predicts HbA1c after hospitalization in patients with type 2 diabetes mellitus. *PLoS One* 2016; 11: e0147303.
12. Haneda M, Noda M, Origasa H, *et al*. Japanese clinical practice guideline for diabetes 2016. *Diabetol Int* 2018; 9: 1–45.
13. Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. *Diabetes Care* 1998; 21: 2191–2192.
14. Matsuo S, Imai E, Horio M, *et al*. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; 53: 982–992.
15. Team RDC. R: A Language and Environment for Statistical Computing. Vienna: R Foundation for Statistical Computing, 2020.
16. Spoto B, Pisano A, Zoccali C. Insulin resistance in chronic kidney disease: a systematic review. *Am J Physiol-Renal Physiol* 2016; 311: F1087–F1108.
17. Lugner M, Gudbjörnsdottir S, Sattar N, *et al*. Comparison between data-driven clusters and models based on clinical features to predict outcomes in type 2 diabetes: nationwide observational study. *Diabetologia* 2021; 64: 1973–1981.
18. Slieker RC, Donnelly LA, Fitipaldi H, *et al*. Replication and cross-validation of type 2 diabetes subtypes based on clinical variables: an IMI-RHAPSODY study. *Diabetologia* 2021; 64: 1982–1989.
19. Koproski J, Pretto Z, Poretsky L. Effects of an intervention by a diabetes team in hospitalized patients with diabetes. *Diabetes Care* 1997; 20: 1553–1555.
20. Maldonado MR, D'Amico S, Rodriguez L, *et al*. Improved outcomes in indigent patients with ketosis-prone diabetes: effect of a dedicated diabetes treatment unit. *Endocr Pract* 2003; 9: 26–32.
21. Healy SJ, Black D, Harris C, *et al*. Inpatient diabetes education is associated with less frequent hospital re-admission among patients with poor glycemic control. *Diabetes Care* 2013; 36: 2960–2967.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Cluster distributions and clinical characteristics (women).

Figure S2 | Distributions of the four clusters except for cluster 1.

Figure S3 | Correlation with previous studies in the intercluster ranking of cluster center coordinates.

Figure S4 | The risk of re-admission for the educational program.

Table S1 | Characteristics of the participants stratified by the conventional classification.

Table S2 | Cluster characteristics.

Table S3 | Cluster center coordinates.

Table S4 | The correlation coefficient of the intercluster rankings of cluster-center coordinates with previous studies.

Table S5 | Multiple linear regression analysis of the level of hemoglobin A1c decline from the educational program.

Table S6 | Cox regression analysis of re-admission risk for the educational program after the discharge.