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ORIGINAL CONTRIBUTIONS

Metabolic Surgery Diabetes Remission (MDR) Score: a New Preoperative Scoring System for Predicting Type 2 Diabetes Remission at 1 Year After Metabolic Surgery in the Singapore Multi-ethnic Asian Setting

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Abstract

Purpose The utility of available scoring systems for type 2 diabetes (T2D) remission prediction after metabolic surgery has not been defined in a multi-ethnic Asian population like Singapore. We sought to assess the predictive performance of the Asia-developed ABCD scoring system for T2D remission after metabolic surgery, and develop a new algorithm to improve prediction.

Materials and Methods We conducted a retrospective analysis of adults with T2D who underwent either Roux-en-Y gastric bypass or sleeve gastrectomy between 2007 and 2018, and followed for 1 year postoperatively ($n = 114$, mean age 46 ± 9 years, 48.2% men, body mass index 40.1 ± 6.6 kg/m^2). The primary outcome was complete T2D remission defined as HbA1c < 6% without the use of anti-diabetic medication at 1 year after surgery.

Results Complete T2D remission was observed in 47.4% of subjects at 1 year post-surgery. Stepwise logistic regression identified preoperative age, T2D duration, HbA1c, and β-cell function (estimated by the homeostasis model) as predictors of complete T2D remission. Based on these four variables, we constructed a new 10-point scoring system named Metabolic surgery Diabetes Remission (MDR) score. Compared with ABCD, MDR produced fewer misclassifications at the mid-high scores, achieving a predictive accuracy of 71–100% at 6 points and above. In addition, MDR achieved a higher area under the receiver operating characteristic curve than ABCD for the primary outcome (0.79 versus 0.67, $P = 0.007$).

Conclusion MDR may serve as a useful clinical scoring system for predicting short-term T2D remission after metabolic surgery in Singapore's multi-ethnic Asian cohort.

Keywords Type 2 diabetes · Roux-en-Y gastric bypass · Sleeve gastrectomy · ABCD · MDR

Introduction

Metabolic surgery is the most effective treatment for type 2 diabetes (T2D) in people with obesity. High-quality evidence from randomized controlled trials has revealed superior benefits of metabolic surgery to intensive medical therapy in improving glycemic control [1, 2]. Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) are currently the most commonly performed surgical therapies for T2D. It is important to note that not all people who undergo metabolic surgery achieve T2D remission. Therefore, identifying preoperative predictors of T2D remission would be of substantial clinical utility as they improve candidate selection for surgery and define realistic postoperative goals.

Several scoring systems have been developed to predict success of T2D remission following metabolic surgery. In

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Asia, Lee et al. constructed the 4-factor ABCD scoring system (age, body mass index (BMI), C-peptide and T2D duration) that is useful for predicting diabetes remission after gastric bypass and SG [3, 4]. The DiaRem score (age, HbA1c, type of anti-diabetic medication, and insulin usage) was subsequently developed based on a predominantly White Caucasian cohort [5]. The Advanced-DiaRem (Ad-DiaRem) score has two additional factors (T2D duration and number of anti-diabetic medication) and modified penalty scores for each category in the original DiaRem [6]. The individualized metabolic surgery score (T2D duration, HbA1c, anti-diabetic medication, and insulin usage) categorizes individuals into 3 stages of diabetes severity, of which mild T2D is associated with the most favorable T2D outcome [7].

The efficacy of the Asia-developed ABCD scoring system for predicting T2D remission has not been previously defined in multi-ethnic Asian populations. In this study, we assessed the predictive performance of the ABCD score for T2D remission after metabolic surgery in Singapore's multi-ethnic Asian setting. Additionally, we devised a new predictive scoring system and compared it with the ABCD score.

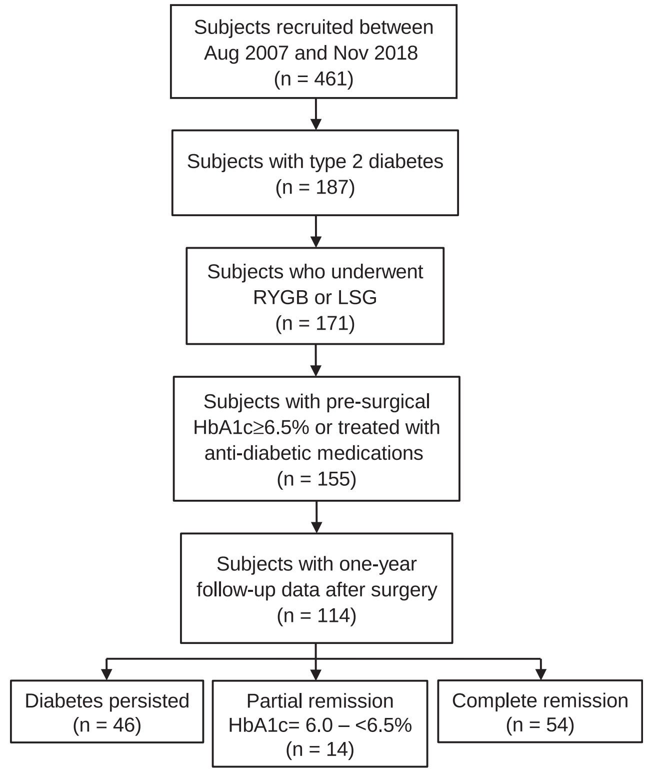


Fig. 1 Flow diagram of patient recruitment, selection, and follow-up

Materials and Methods

Subjects

Adults scheduled for metabolic surgery were recruited between August 2007 and November 2018 (Fig. 1). This retrospective study included people with T2D who underwent either RYGB or SG, and had preoperative HbA1c of $\geq 6.5\%$ or treated with anti-diabetic medication ($n = 114$). Subjects who had preoperative HbA1c $< 6.5\%$ without anti-diabetic medication (i.e. unlikely to have diabetes at baseline), had surgeries other than RYGB or SG, or were lost to 1-year follow-up were excluded from the analysis. Information on medical history and medication in use was recorded by a questionnaire.

Anthropometric and Biochemical Measurements

Height and weight were measured by standard procedure, and BMI was computed as weight (in kg) divided by height (in m^2). Percentage of total body weight loss was calculated as 100 × (preoperative weight – postoperative weight) / preoperative weight. HbA1c was measured using a point-of-care immunoassay analyzer certified by the National Glycohaemoglobin Standardization Programme (DCA Vantage Analyser; Siemens Healthcare Diagnostics, Erlangen, Germany). Fasting plasma glucose concentrations were measured by the glucose-oxidase technique. The fasting C-peptide levels were measured using sandwich chemiluminescence immunoassay. The lowest detection limit is 17 pmol/L, and the total imprecision ranges from 1.9 to 4.6% for a concentration range of 346–4643 pmol/L. The homeostasis model assessment (HOMA) indexes were estimated from the fasting plasma glucose and C-peptide concentrations by using the online-available HOMA2 calculator [8].

ABCD Diabetes Surgery Score System

As described by Lee et al. [4], this simple 10-point scoring system integrates age, BMI, C-peptide, and duration of diabetes. While age uses a 2-point scale (years; $\geq 40 = 0$, $< 40 = 1$), BMI (kg/m^2; $< 27 = 0$, $27–34.9 = 1$, $35–41.9 = 2$, $\geq 42 = 3$), c-peptide (ng/ml; $< 2 = 0$, $2–2.9 = 1$, $3–4.9 = 2$, $\geq 5 = 3$), and diabetes duration (years; $> 8 = 0$, $4–8 = 1$, $1–3.9 = 2$, $< 1 = 3$) use a 4-point scale. A high ABCD score implies higher probability of T2D remission after metabolic surgery.

Statistical Analysis, Definitions, and Development of the Prediction Algorithm

The statistical analyses were performed using the STATA software version 14 (Stata Corporation, College Station, TX, USA) and SPSS version 22 (IBM Corp, NY, USA). Continuous variables were presented as mean ± SD or median (interquartile range), and categorical data were presented as n (%). Parametric Student's t test and non-parametric Mann-Whitney test statistical tests were employed for comparison of continuous variables between groups. Chi-square test was used to compare categorical variables. Backward stepwise logistic regression with a P value inclusion threshold of 0.1 was performed to identify predictors of complete T2D remission defined as HbA1c < 6% without use of anti-diabetic medication at 1 year after metabolic surgery [4]. Partial T2D remission was defined as 1-year postoperative HbA1c of between 6 and < 6.5%, irrespective of use of anti-diabetic medication. The Metabolic surgery Diabetes Remission (MDR) score was developed based on the variables retained in the final stepwise logistic regression model. Taking into consideration variable informativeness, the components of MDR that had $P < 0.05$ in the final stepwise regression model (HbA1c and T2D duration) were assigned a score ranging from 0 to 3 as guided by quartile cut-offs, whereas those that were marginally significant (age and HOMA-B) were graded a score ranging from 0 to 2 as guided by tertile cut-offs. The points for each component were added, and the total possible score ranged from 0 to 10 points. The diagnostic accuracy of MDR and ABCD scores was assessed using receiver operating characteristic (ROC) curves, and the areas under the ROC curves (AUC) were compared using the DeLong method [9]. In addition, the sensitivity, specificity, positive predictive value, negative predictive value, and optimal cut-off by highest Youden index [10] were calculated.

Results

Characteristics of Subjects

Table 1 shows the preoperative characteristics of the participants subgrouped by 1-year complete T2D remission status ($n = 114$). Compared with the non-remitters (12.3% partial remission and 40.4% persistent T2D), the remitters (47.4%) had younger age and shorter T2D duration. Those who responded favorably also displayed better preoperative glycaemic control and β-cell function (HOMA-B). At 1 year post-surgery, the HbA1c levels of non-remitters and remitters were 6.8 ± 1.2% and 5.5 ± 0.3%, respectively ($P < 0.001$). Despite having similar preoperative BMI, the remitters experienced greater 1 year percentage of total weight loss than the non-remitters (27.7 ± 7.3% versus 20.8 ± 7.5%, $P < 0.001$).

Predictive Ability of the ABCD Score

We assessed the predictive accuracy of the ABCD score in our cohort (Table 2). None of the participants obtained a score of 0 or 10 points. At high scores of 8–9, correct prediction of complete T2D remission was 100%. However, at mid-high scores of 6 and 7, the accuracy of correctly predicting complete T2D remission was 50–56%. Expectedly, misclassifications were

Table 1 Baseline subject characteristics subgrouped by diabetes remission status post-metabolic surgery

Variable	Total ($n = 114$)	Non-remitters ($n = 60$)	Remitters ($n = 54$)	P value
Age (years)	46 ± 9	48 ± 10	44 ± 8	0.013
Men, n (%)	55 (48.2)	24 (40.0)	31 (57.4)	0.063
Ethnicity, n (%)				
Chinese	37 (32.4)	21 (35.0)	16 (29.6)	0.659
Malay	46 (40.4)	25 (41.7)	21 (38.9)	
Indian	20 (17.5)	8 (13.3)	12 (22.2)	
Others	11 (9.6)	6 (10.0)	5 (9.3)	
BMI (kg/m^2)	40.1 ± 6.6	39.9 ± 7.2	40.3 ± 5.9	0.736
FPG (mmol/L)[a]	9.7 ± 3.7	10.6 ± 3.7	8.6 ± 3.3	0.005
HbA1c (%)	8.8 ± 1.9	9.4 ± 2.0	8.1 ± 1.6	< 0.001
Diabetes duration (years)	6 (2–10)	9 (6–12)	3 (1–6)	< 0.001
Hypertension, n (%)	89 (78.1)	47 (78.3)	42 (77.8)	0.943
Hyperlipidaemia, n (%)	98 (86.0)	57 (95.0)	41 (75.9)	0.003
C-peptide (ng/ml)	3.1 (2.0–3.9)	2.7 (1.6–3.9)	3.3 (2.3–3.9)	0.136
HOMA-IR[a]	2.7 (1.7–3.6)	2.6 (1.6–3.8)	2.7 (1.9–3.2)	0.882
HOMA-B (%)[a]	55.0 (27.0–90.6)	42.0 (22.9–87.1)	76.8 (43.0–107.5)	0.005
Medications, n (%)				
OHGA	103 (90.4)	54 (90.0)	49 (90.7)	0.894
Insulin	42 (36.8)	33 (55.0)	9 (16.7)	< 0.001
Anti-hypertensives	75 (65.8)	42 (70.0)	33 (61.1)	0.318
Lipid-lowering	85 (74.6)	52 (86.7)	33 (61.1)	0.002
Surgery, n (%)				
RYGB	80 (70.2)	38 (63.3)	42 (77.8)	0.092
SG	34 (29.8)	22 (36.7)	12 (22.2)	

BMI, body mass index; *FPG*, fasting plasma glucose; *HOMA-IR*, homeostasis model assessment of insulin resistance; *HOMA-B*, homeostasis model assessment of β-cell function; *OHGA*, oral hypoglycaemic agent; *RYGB*, Roux-en-Y gastric bypass; *SG*, laparoscopic sleeve gastrectomy

[a] $n = 108$ (58 non-remitters versus 50 remitters)

Table 2 Predictive performance of ABCD for T2D remission at 1-year follow-up

ABCD score	*n*	Complete T2D remission (*n*)	Complete T2D remission (%)	Partial/ complete T2D remission (*n*)	Partial/ complete T2D remission (%)
0	0	0	-	0	-
1	8	2	25	2	25
2	13	2	15.4	3	23.1
3	9	4	44.4	4	44.4
4	20	8	40	10	50
5	17	10	58.8	13	76.5
6	18	10	55.6	14	77.8
7	22	11	50	15	68.2
8	6	6	100	6	100
9	1	1	100	1	100
10	0	0	-	0	-
Total	114	54		68	

less frequent when predicting partial/complete T2D remission.

Development and Performance of MDR

Backward stepwise logistic regression analysis with complete T2D remission as the outcome was performed using candidate variables selected from the univariate test shown in Table 1 (age, gender, T2D duration, HbA1c, HOMA-B, insulin usage). Of note, HOMA-B could not be computed for 6 people due to missing fasting glucose data. Hence, the cohort size analyzed was 108. The final model retained four independent predictors: age (odds ratio (OR), 0.95; 95% CI, 0.90–1.00; $P = 0.054$), T2D duration (OR, 0.88; 95% CI, 0.81–0.97; $P = 0.006$), HbA1c (OR, 0.72; 95% CI, 0.55–0.94; $P = 0.016$), and HOMA-B (OR, 1.07; 95% CI, 1.00–1.02; $P = 0.099$). Using the four variables, we devised the MDR scoring system as described in methods (Table 3). A MDR score of 6 points and higher yielded a prediction accuracy ranging from 83 to 100% and 71 to 100% for partial/complete and complete T2D remission, respectively (Table 4). Moreover, the discriminative ability of MDR to identify complete T2D remission was significantly greater than ABCD (Fig. 2; AUC 0.79 versus 0.67, $P = 0.007$). As determined by the highest Youden index, the optimal MDR cut-off score was ≥ 4 points, yielding a sensitivity of 76% and specificity of 70.7%.

Table 3 Variables and score used to calculate MDR

MDR	0	1	2	3
Age (years)	> 50	41–50	≤ 40	-
HOMA2-B (%)	≤ 40	> 40–80	> 80	-
DM duration (years)	≥ 10	6–9	2–5	< 2
HbA1c (%)	≥ 10	8.5–< 10	7.0–< 8.5	< 7

Discussion

Not all people with obesity achieve complete T2D remission after metabolic surgery. In our cohort, 47.4% of subjects experienced complete T2D remission at 1 year after metabolic surgery, while 12.3% had partial remission. Consistently, a retrospective analysis of 134 individuals who underwent RYGB revealed that 15.7% and 46.1% achieved partial and complete T2D remission during a mean follow-up of 12 months, respectively, and a non-remission rate of 38.2% [11]. Given the invasive nature of metabolic surgery, it is important to identify patients who can best benefit from surgery.

The ABCD score is a prediction algorithm of T2D remission developed in Asia [3, 4]. Although limited, the efficacy of ABCD has been tested in several Asian populations that are ethnically homogeneous. A Japanese study showed that the ROC curve of the ABCD score for T2D remission had an AUC of 0.79 [12]. More recently, Kam et al. demonstrated in Chinese adults that the AUC values of ABCD in predicting T2D remission after RYGB at 1-year and 3-year follow-up were 0.74 and 0.75, respectively [13]. The performance of ABCD in multi-ethnic Asian populations had not been previously reported. In our mixed ethnic cohort, we observed frequent misclassifications at mid-high ABCD scores. Moreover, the AUC obtained by our cohort was 0.67. The reduced discriminative ability of ABCD could be partly explained by the variability in adiposity and insulin sensitivity in different Asian ethnic groups [14]. Moreover, the cohort involved for ABCD construction had a clinical profile different from our cohort [3, 4]. Our participants generally had older age and longer T2D duration, suggesting a poorer β-cell reserve. While obesity is a feature of the ABCD score, we did not observe a marked difference in preoperative BMI between remitters and non-remitters of T2D (Table 1). Evolving body of evidence suggests that the susceptibility to obesity-associated metabolic complications is not mediated by the amount of fatness per se, but by the inability for excess energy to be stored appropriately in adipose tissue after reaching an individual's fat threshold [15, 16]. In the face of sustained excessive nutrition, exhaustion of adipose tissue expandability creates stress on adipocytes and elicits a maladaptive inflammatory response over time, eventually causing insulin resistance and T2D [16]. Therefore, BMI alone may not sufficiently capture this concept of maladaptive excess adiposity.

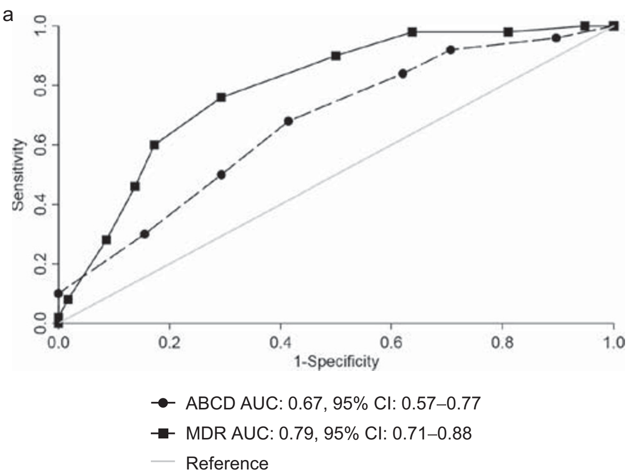
In order to improve the prediction of T2D remission following metabolic surgery in our multi-ethnic cohort, we developed a new scoring algorithm (MDR). Like the ABCD [3, 4], MDR is a 4-factor 10-point scoring system, with higher scores predicting

Table 4 Predictive performance of MDR for T2D remission at 1-year follow-up

MDR	*n*	Complete T2D remission (*n*)	Complete T2D remission (%)	Partial/complete T2D remission (*n*)	Partial/complete T2D remission (%)
0	3	0	0	1	33.3
1	9	1	11.1	3	33.3
2	10	0	0	0	0
3	12	4	33.3	6	50
4	19	7	36.8	9	47.4
5	15	8	53.3	8	53.3
6	9	7	77. 8	8	88.9
7	12	9	75	10	83.3
8	14	10	71.4	13	92.9
9	4	3	75	4	100
10	1	1	100	1	100
Total	108	50		63	

higher probability of diabetes remission. We demonstrated that MDR outperformed ABCD in our cohort, yielding a reasonable discriminative power of 0.79. At a score of 6 and above, MDR yielded a predictive accuracy of complete T2D remission ranging from 71 to 100%. However, the utility of MDR for predicting long-term T2D remission warrants further investigation.

a



b

Model	ABCD	MDR
Cut-off	≥4	≥4
Sensitivity (%)	70.4	76
Specificity (%)	56.7	70.7
PPV (%)	59.4	69.1
NPV (%)	68	77.4
Youden index	27.1	46.7

PPV: positive predictive value, NPV: negative predictive value

Fig. 2 Discriminative ability of ABCD and MDR. **a** ROC curves and AUC. **b** Optimal cut-off scores, sensitivity, specificity, positive predictive value, negative predictive value, and Youden index for each model

The MDR, consisting of age, T2D duration, HbA1c, and HOMA-B, devotes great emphasis on pancreatic islet cell involvement. Specifically, age reflects the general reserve of β-cell function; T2D duration is a proxy for natural course and deterioration of β-cell function; HbA1c is associated with insulin secretion; and HOMA-B reflects β-cell secretory activity in response to plasma glucose concentrations [17, 18]. This supports that better-preserved pancreatic β-cell reserve is critical for facilitating amelioration of T2D after metabolic surgery. People with diminished β-cell reserve may not have the capacity to synthesize and secrete an adequate concentration of insulin to restore glycaemic control [19, 20]. Usage of insulin, which reflects T2D severity, is a common component of the DiaRem, Ad-DiaRem, and individualized metabolic surgery score [5–7]. Although our data showed that insulin usage was significantly different between non-remitters and remitters (Table 1), the variable was not retained as an independent predictor of T2D remission in the stepwise regression model, possibly due to considerable association with HbA1c and T2D duration.

Our work included subjects who underwent either RYGB or SG. We observed that a higher proportion of individuals who underwent RYGB than SG achieved complete diabetes remission (Table 1; 52.5% versus 35.3%), but the difference was not statistically significant ($P = 0.092$). Consistently, the 1-year data from the Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial showed that RYGB did not differ from SG in terms of complete diabetes remission (42% versus 27%, respectively, $P = 0.10$) [21]. Similarly, the 5-year data from the Finnish Sleeve vs Bypass (SLEEVEPASS) and Swiss Multicenter Bypass or Sleeve Study (SM-BOSS) trials reported comparable rates of complete T2D remission between RYGB and

SG [22, 23]. Nevertheless, it is notable that the short- and long-term analysis of the STAMPEDE trial revealed more individuals in the RYGB group achieving the primary endpoint target of HbA1c < 6% without the use of anti-diabetic medication than those in the SG group [2, 21]. These findings demonstrate superiority of RYGB over SG in T2D reversal.

To our knowledge, this study is the first of its kind in multiethnic Asian populations. However, we acknowledge several limitations including the retrospective design and short follow-up. In addition, the small sample size limits ethnic subgroup analysis. The proportion of SG is considerably lower than RYGB; thus, the comparison between the two procedures may not be robust. Our medication data lack granularity. Hence, the performance of other available scoring systems such as DiaRem and Ad-DiaRem could not be assessed in our cohort. Loss to follow-up, typically consisting of younger subjects with less severe T2D condition (i.e. shorter T2D duration and lower HbA1c), may bias the results. Our findings were not validated in an independent cohort and may not be generalizable beyond this study population.

Conclusion

In this study, we have devised a clinically useful algorithm MDR that outperforms ABCD score for predicting T2D remission at 1 year after metabolic surgery in Singapore's multiethnic Asian cohort.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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