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Real-world data reveal unmet clinical needs in insulin treatment in Asian people with type 2 diabetes: the Joint Asia Diabetes Evaluation (JADE) Register

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Abstract

Aims: To explore the pattern of insulin use and glycaemic control in Asian people with type 2 diabetes, stratified by gender, young-onset diabetes (YOD; diagnosed before age 40 years), and diabetic kidney disease (DKD; estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73m^2).

Materials and methods: We conducted a cross-sectional analysis of 97 852 patients from 11 Asian countries/regions (2007–2017) included in the prospective Joint Asia Diabetes Evaluation (JADE) Register.

Results: Among 18 998 insulin users (47% women, mean ± SD age 59.2 ± 11.7 years, diabetes duration 13.2 ± 8.3 years, glycated haemoglobin [HbA1c] 72 ± 21.4 mmol/mol [8.74 ± 1.95%], median total daily insulin dose [TDD] 0.27–0.82 units/kg), 25% and 29.5% had YOD and DKD, respectively. Premixed (44%) and basal-only (42%) insulin were the most common regimens. Despite being more commonly treated with these two regimens with higher insulin dosages, patients with YOD had worse HbA1c levels than their late-onset peers (73 ± 20.5 vs. 71 ± 21.2 mmol/mol [8.82 ± 1.87% vs. 8.66 ± 1.94%]; $P < 0.001$). Fewer women than men attained an HbA1c level < 53 mmol/mol (7%; 15.7% vs 17.1%; $P = 0.018$). Adjusting for age, diabetes duration, TDD, HbA1c, eGFR, and use of oral glucose-lowering drugs at baseline, the odds of self-reported hypoglycaemia were higher in women (vs. men: adjusted odds ratio [aOR] 1.16, 95% confidence interval [CI] 1.05–1.28) and in patients with DKD treated with a premixed regimen (1.81 [95% CI 1.54–2.13] vs. 1.34 [95% CI 1.16–1.54] in non-DKD; $P_{interaction} < 0.001$). Compared to basal-only regimens, premixed and basal-bolus regimens had similar HbA1c reductions but were

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independently associated with increased odds of hypoglycaemia (1.65 [95% CI 1.45–1.88] and 1.88 [95% CI 1.58–2.23], respectively).

Conclusions: In this Asian population, there were varying patterns of insulin regimens with suboptimal glycaemic control, despite relatively high TDDs, which were influenced by gender, DKD, and YOD status.

KEYWORDS
Asians, hypoglycaemia, insulin therapy, nephropathy, type 2 diabetes, women, young-onset diabetes

1 | INTRODUCTION

More than half of the population with diabetes live in Asia and the largest increases in prevalence are estimated to be in the Western Pacific and South-East Asia regions.[1] β-cell dysfunction plays a key role in the development of diabetes in Asians with intermediate hyperglycaemia.[2] The low body mass index (BMI) in Asian people is often accompanied by low β-cell function, putting them at high risk of progression to type 2 diabetes, especially in the presence of obesity.[3,4]

Each individual with diabetes has a unique profile, with age and gender having independent effects on risk profiles, psychosocial needs, and health-related behaviours, which may influence clinical course. While age is a major risk factor for type 2 diabetes, young-onset diabetes (YOD; diagnosed before the age of 40 years) now affects one in five Asian adults.[5] Apart from genetic predisposition, lifestyle and environmental factors, such as exposure to endocrine-disrupting pollutants, can induce oxidative stress and strain the pancreatic β cells, increasing the risk of YOD.[6,7] In a territory-wide diabetes surveillance database of more than 0.4 million adults with diabetes in Hong Kong, 17% had YOD and spent, on average, 100 nights in hospital before the age of 75 years as a result of cardiovascular-renal diseases, mental illness, and sepsis.[8] As many as 20% to 50% of people with type 2 diabetes may experience anxiety, stress, and/or depression, especially women and people with YOD, which may negatively impact adherence with increased risk of poor glycaemic control and hypoglycaemia.[8,9] While we observed variations in the attainment of treatment goals across countries, there are persistent care gaps in people with YOD, who often require insulin early. In these patients with long disease duration, a suboptimal cardiometabolic risk profile can lead to 1.2 to 1.6 times higher risk of cardiovascular-renal diseases and premature deaths at any given age, compared to their late-onset peers.[5,10-12]

Epidemiological surveys and randomized clinical trials have reported a high prevalence of diabetic kidney disease (DKD) in Asia, affecting one in six adults with type 2 diabetes.[13-15] In the Hong Kong Renal Register, while 60% of patients receiving renal replacement therapy (RRT) had diabetes as a cause, the most rapid rate of increase of RRT occurred in the age group 45 to 60 years, highlighting the long-term burden of YOD.[16] In people with DKD, dose adjustment or discontinuation of oral glucose-lowering drugs, such as metformin and sulphonylureas, because of side effects, is often followed by initiation of insulin therapy.[17]

Given the high prevalence of YOD and DKD in Asia, as well as the potential effects of gender differences in clinical outcomes, we used a multinational, real-world diabetes register with documentation of clinical and biochemical characteristics using the same protocol to explore the patterns of insulin use and the associations of different insulin regimens with glycaemic control in Asians with type 2 diabetes, stratified by gender, YOD, and DKD status at baseline. We hypothesized that a premixed regimen was associated with lower glycated haemoglobin (HbA1c) level but with higher risk of hypoglycaemia than other insulin regimens in Asian people with type 2 diabetes.

2 | MATERIALS AND METHODS

We conducted a cross-sectional study based on a prospective type 2 diabetes cohort recruited from the Joint Asia Diabetes Evaluation (JADE) Register. The latter is a web-based structured diabetes care programme in Asia set up since 2007.[18] It consists of a portal with built-in protocols to guide data collection during structured comprehensive assessment (blood/urine tests and eye/foot examination), performed every 12 to 24 months as recommended by most guidelines.[19] Apart from enabling the physicians to establish a diabetes register for quality improvement, the data are used to estimate the 5-year probability of major clinical events using validated risk equations, followed by issue of personalized reports with decision support to empower shared decision-making between physicians and patients. Since its inception, 332 sites from 11 countries/regions across Asia have registered patients with diabetes into the JADE Register. Among them, 60% and 24% were hospital- and community-based clinics, respectively. Table S1 shows the healthcare settings of various study sites by countries/regions. To our knowledge, the JADE Register is the first large-scale quality improvement programme to establish an online, real-world database in Asia to advance our understanding of the clinical course and health outcomes in Asian people with diabetes.

All JADE participants underwent detailed clinical evaluation including documentation of sociodemographic data, lifestyle and self-management, history of comorbidities, current medications (dosage

and hypoglycaemia, if any), as well as anthropometric measurements and examination for diabetes-related complications.[18] Participants were considered to have cardiovascular disease (CVD) if they reported a history of coronary heart disease, cerebrovascular disease, or peripheral vascular disease (based on revascularization or ankle-brachial index ≤0.9). Blood and urine samples were collected after 8 to 10 hours of fasting.

In the present analysis, we included data from Asian people with type 2 diabetes aged ≥18 years treated with insulin on registration in the JADE Register between January 1, 2007 and October 31, 2017. Exclusion criteria were: 1) type 1 diabetes, defined as presentation with either diabetic ketoacidosis, unprovoked ketosis, or continuous insulin requirement within 12 months of diagnosis and 2) treatment with either diet/exercise or oral glucose-lowering drugs only. We defined YOD as a diagnosis of type 2 diabetes before the age of 40 years[5] and DKD based on estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 derived from the creatinine-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[20]

We assessed the frequency and severity of self-reported hypoglycaemia in the past 3 months according to the following: 1) experience of typical symptoms of hypoglycaemia (such as hunger, dizziness, perioral numbness, tremor especially if corrected by carbohydrate intake); 2) frequency of hypoglycaemia (at least daily, at least once weekly, at least once monthly, or less than once monthly); 3) nature of the hypoglycaemic episode (mild, moderate, or severe in terms of impairment of daily activities); and 4) number of severe hypoglycaemic episodes requiring attention by a third party, including medical personnel. All participants gave written informed consent for analysis and reporting of the anonymized data. The study was approved by the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee.

2.1 | Statistical analysis

Data are presented as mean ± SD or median (interquartile range [IQR]) for continuous variables with normal or skewed distribution, respectively. Categorical variables are expressed as number and percentages. For continuous variables, we used independent *t*- or Wilcoxon rank-sum tests for comparing two groups, and one-way ANOVA or the Kruskal–Wallis test for comparing three groups or more. We used the chi-squared test for between-group comparisons of categorical variables.

We performed multivariable linear regression analyses to examine the association between HbA1c and insulin regimens using basal-only regimen as the reference. We adjusted for age, sex, duration of diabetes, country/region, history of CVD, logarithmically transformed and weight-adjusted total daily insulin dose (TDD), eGFR, and use of oral glucose-lowering drugs at baseline, as appropriate. Weight-adjusted TDD is calculated by dividing the total daily basal and bolus insulin dosage by body weight, and expressed in units/kg/d. In the logistic regression analyses where hypoglycaemia (at least once monthly) was the dependent variable, apart from the aforementioned covariables, we also adjusted for HbA1c at baseline. The results were presented as adjusted beta coefficients (β) or adjusted odds ratios (aORs) with 95% confidence intervals (CIs). We tested the modifying effects of gender, YOD (yes/no), and DKD (yes/no) with insulin regimens, on HbA1c and risk of hypoglycaemia using each cross-product term in the regression models, followed by stratified analyses. All statistical tests were conducted using R 3.5.1 (www.r-project.org). A two-sided *P* value <0.05 was considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics

Between 2007 and 2017, 108 637 patients with diabetes (90% had type 2 diabetes) from 11 Asian countries/regions were enrolled in the JADE Register. Among patients with type 2 diabetes, 20 031 were insulin-users, of whom 18 998 had complete insulin data for analysis (Figure S1). Table 1 and Table S2 show the baseline characteristics of the study cohort, stratified by gender, YOD, and DKD at baseline. In the analysed cohort (mean ± SD age 59.2 ± 11.7 years, HbA1c 72 ± 21.4 mmol/mol [8.74 ± 1.95%], BMI 26.3 ± 4.6 kg/m^2, duration of diabetes 13.2 ± 8.3 years), 47% were women, 24.8% had YOD, and 29.5% had DKD. A total of 44%, 42%, and 10% of the cohort were treated with premixed, basal-only, and basal-bolus regimens, respectively. Nearly 50% of the cohort were treated with organ-protective drugs such as renin-angiotensin system inhibitors and statins. More than 80% of these patients performed self-monitoring of blood glucose.

Compared to men, more women had DKD but with a lower proportion for CVD or HbA1c <53 mmol/mol (7%). The weight-adjusted TDD was also higher in women. Patients with YOD had a higher BMI and a higher proportion of them received basal-bolus and premixed insulin regimens, with a higher weight-adjusted TDD than those with late-onset diabetes. More patients with DKD had coexistent CVD and were treated with premixed insulin than patients without DKD.

3.2 | Patterns of insulin use in Asia

Upon stratification by type of insulin regimen, premixed regimen was the preferred regimen in most countries/regions (China, India, Singapore, Philippines, Taiwan, Thailand, and Vietnam; Table S3). Basal-only regimens were most commonly prescribed in Hong Kong, Korea, Indonesia and Malaysia, although basal-bolus regimens were also popular in the latter two countries. The median (IQR) weight-adjusted TDD was 0.60 (0.42–0.90) units/kg/d for premixed regimen and ranged from 0.27 to 0.82 units/kg/d for basal-only, bolus-only, and basal-bolus regimens.

3.3 | Quality of glycaemic control

In multivariable linear regression analyses, compared to basal-only, the HbA1c reduction was similar with the use of basal-bolus,

TABLE 1 Baseline characteristics of the study cohort, stratified by gender, young-onset diabetes, and diabetic kidney disease (DKD) at baseline

	All patients (n = 18 998)		Gender					Onset of diabetes					DKD at baseline				
				Men (n = 10 047)		Women (n = 8951)	*P*	Young-onset (age of diagnosis <40 years; n = 4705)		Late-onset (age of diagnosis ≥40 years; n = 13 247)		*P*	Yes (eGFR< 60 mL/min/1.73 m^2; n = 5601)		No (eGFR≥60 mL/min/ 1.73 m^2; n = 13 397)		*P*
	n		n		n			n		n			n		n		
Age, years	18 998	59.2 ± 11.7	10 047	58.5 ± 11.7	8951	59.9 ± 11.6	<0.001	4705	52.0 ± 8.4	13 247	63.3 ± 9.3	<0.001	5601	65.1 ± 10.3	13 397	56.7 ± 11.3	<0.001
Women, n (%)	18 998	8951 (47.1)	NA	NA	NA	NA	NA	4705	2097 (44.6)	13 247	6379 (48.2)	<0.001	5601	2764 (49.3)	13 397	6187 (46.2)	<0.001
Duration of diabetes, years	17 952	13.2 ± 8.3	9476	12.9 ± 8.3	8476	13.5 ± 8.3	<0.001	4705	17.8 ± 9.0	13 247	11.5 ± 7.4	<0.001	5488	15.4 ± 8.5	12 464	12.2 ± 8.0	<0.001
HbA1c, NGSP (%)	17 150	8.74 ± 1.95	9176	8.74 ± 1.99	7974	8.75 ± 1.92	0.680	4317	8.82 ± 1.87	11 890	8.66 ± 1.94	<0.001	5255	8.48 ± 1.86	11 895	8.86 ± 1.98	<0.001
HbA1c, IFCC (mmol/mol)	17 150	72 ± 21.4	9176	72 ± 21.7	7974	72 ± 21.0	0.680	4317	73 ± 20.5	11 890	71 ± 21.2	<0.001	5255	69 ± 20.3	11 895	74 ± 21.7	<0.001
HbA_{1c} < 7% (53 mmol/mol)	17 150	2823 (16.5)	9176	1568 (17.1)	7974	1255 (15.7)	0.018	4317	607 (14.1)	11 890	2091 (17.6)	<0.001	5255	1036 (19.7)	11 895	1787 (15.0)	<0.001
Systolic BP, mmHg	18 697	134 ± 18.5	9905	133 ± 18.1	8792	134 ± 18.9	0.006	4643	133 ± 17.5	13 036	135 ± 18.7	<0.001	5560	139 ± 19.5	13 137	131 ± 17.5	<0.001
Diastolic BP, mmHg	18 665	78.1 ± 10.0	9888	79.1 ± 9.8	8777	77.1 ± 10.0	<0.001	4633	78.6 ± 9.7	13 018	78.0 ± 10.1	0.001	5550	78.2 ± 10.3	13 115	78.1 ± 9.8	0.710
Total cholesterol, mmol/L	15 691	4.6 ± 1.2	8248	4.5 ± 1.2	7443	4.8 ± 1.2	<0.001	3908	4.6 ± 1.1	10 953	4.6 ± 1.2	0.583	4890	4.6 ± 1.2	10 801	4.7 ± 1.2	0.029
LDL cholesterol, mmol/L	16 191	2.6 ± 1.2	8620	2.6 ± 1.2	7571	2.7 ± 1.2	<0.001	4048	2.6 ± 1.1	11 303	2.6 ± 1.2	0.017	5055	2.7 ± 1.3	11 136	2.6 ± 1.1	0.055
HDL cholesterol, mmol/L	16 256	1.2 ± 0.4	8628	1.1 ± 0.4	7628	1.3 ± 0.4	<0.001	4056	1.2 ± 0.4	11 351	1.2 ± 0.4	0.101	5085	1.2 ± 0.4	11 171	1.2 ± 0.4	<0.001
Triglycerides, mmol/L	16 443	1.5 (1.1–2.1)	8766	1.5 (1.0–2.1)	7677	1.5 (1.1–2.1)	0.840	4100	1.5 (1.0–2.1)	11 485	1.5 (1.1–2.1)	0.888	5167	1.7 (1.2–2.2)	11 276	1.5 (1.0–2.1)	<0.001
BMI, kg/m^2	18 335	26.3 ± 4.6	9734	26.1 ± 4.3	8601	26.5 ± 4.9	<0.001	4580	26.8 ± 4.8	12 780	26.1 ± 4.5	<0.001	5455	26.5 ± 4.4	12 880	26.1 ± 4.7	<0.001
eGFR, mL/min/ 1.73 m^2	16 546	74.5 ± 28.0	8882	75.5 ± 28.0	7664	73.4 ± 28.0	<0.001	4137	81.9 ± 26.7	11 553	69.9 ± 26.7	<0.001	5590	42.0 ± 15.6	10 956	91.0 ± 15.8	<0.001
Urine ACR, mg/mmol	10 795	4.2 (1.1–24.0)	5689	4.3 (1.0–26.4)	5106	4.1 (1.2–21.8)	0.840	2747	3.7 (0.9–21.2)	7520	4.7 (1.2–26.0)	0.733	3347	18.5 (3.7–99.2)	7448	2.6 (0.8–11.4)	<0.001
Current smoker, n (%)	18 722	2025 (10.8)	9926	1877 (18.9)	8796	148 (1.7)	<0.001	4645	521 (11.2)	13 062	1369 (10.5)	0.172	5541	389 (7.0)	13 181	1636 (12.4)	<0.001
CVD, n (%)	18 998	4386 (23.1)	10 047	2612 (26.0)	8951	1774 (19.8)	<0.001	4705	818 (17.4)	13 247	3488 (26.3)	<0.001	5601	1974 (35.2)	13 397	2412 (18.0)	<0.001
DKD, n (%)	18 998	5601 (29.5)	10 047	2837 (28.2)	8951	2764 (30.9)	<0.001	4705	1037 (22.0)	13 247	4451 (33.6)	<0.001	NA	NA	NA	NA	NA
Insulin regimen, n (%)	18 998		10 047		8951		0.105	4705		13 247		<0.001	5601		13,397		0.002

(Continues)

TABLE 1 (Continued)

	All patients (n = 18 998)		Gender					Onset of diabetes					DKD at baseline				
				Men (n = 10 047)		Women (n = 8951)	*P*	Young-onset (age of diagnosis <40 years; n = 4705)		Late-onset (age of diagnosis ≥40 years; n = 13 247)		*P*	Yes (eGFR< 60 mL/min/1.73 m^2; n = 5601)		No (eGFR≥60 mL/min/ 1.73 m^2; n = 13 397)		*P*
	n		n		n			n		n			n		n		
Basal only		7905 (41.6)		4128 (41.1)		3777 (42.2)			1737 (36.9)		5778 (43.6)			2267 (40.5)		5638 (42.1)	
Basal-bolus		1927 (10.1)		1055 (10.5)		872 (9.7)			630 (13.4)		1131 (8.5)			551 (9.8)		1376 (10.3)	
Bolus-only		829 (4.4)		459 (4.6)		370 (4.1)			210 (4.5)		565 (4.3)			216 (3.9)		613 (4.6)	
Premixed		8337 (43.9)		4405 (43.8)		3932 (43.9)			2128 (45.2)		5773 (43.6)			2567 (45.8)		5770 (43.1)	
Total daily insulin dose, units/kg/d																	
Basal-only	6961	0.27 (0.18–0.45)	3669	0.25 (0.16–0.41)	3292	0.30 (0.19–0.49)	<0.001	1513	0.30 (0.19–0.49)	5104	0.27 (0.17–0.44)	<0.001	1965	0.29 (0.18–0.47)	4996	0.27 (0.18–0.44)	0.018
Basal-bolus	1715	0.82 (0.52–1.28)	945	0.79 (0.51–1.26)	770	0.85 (0.54–1.29)	0.119	568	0.89 (0.57–1.39)	995	0.80 (0.50–1.24)	0.002	489	0.89 (0.54–1.31)	1226	0.79 (0.52–1.26)	0.080
Bolus-only	726	0.58 (0.35–0.91)	401	0.56 (0.34–0.89)	325	0.61 (0.36–0.91)	0.240	180	0.59 (0.38–0.94)	497	0.58 (0.33–0.92)	0.333	192	0.61 (0.35–0.98)	534	0.56 (0.35–0.87)	0.256
Premixed	7090	0.60 (0.42–0.90)	3860	0.55 (0.39–0.84)	3230	0.65 (0.45–0.96)	<0.001	1823	0.67 (0.44–1.00)	4900	0.58 (0.41–0.86)	<0.001	2156	0.60 (0.44–0.87)	4934	0.60 (0.40–0.91)	0.425
On oral glucose-lowering drugs, n (%)	18 998	14 292 (75.2)	10 047	7427 (73.9)	8951	6865 (76.7)	<0.001	4705	3801 (80.8)	13 247	9793 (73.9)	<0.001	5601	3598 (64.2)	13 397	10 694 (79.8)	<0.001
On RAS inhibitors, n (%)	18 998	8945 (47.1)	10 047	4761 (47.4)	8951	4184 (46.7)	0.383	4705	2240 (47.6)	13 247	6466 (48.8)	0.161	5601	3299 (58.9)	13 397	5646 (42.1)	<0.001
On statins, n (%)	18 998	9354 (49.2)	10 047	4994 (49.7)	8951	4360 (48.7)	0.175	4705	2345 (49.8)	13 247	6707 (50.6)	0.361	5601	3287 (58.7)	13 397	6067 (45.3)	<0.001
SMBG, n (%)	17 663	14 684 (83.1)	9288	7740 (83.3)	8375	6944 (82.9)	0.469	4388	3697 (84.3)	12 337	10 262 (83.2)	0.106	5310	4557 (85.8)	12 353	10 127 (82.0)	<0.001
Self-reported hypoglycaemia (at least once monthly), n (%)	17 793	3112 (17.5)	9379	1633 (17.4)	8414	1479 (17.6)	0.785	4432	846 (19.1)	12 409	2148 (17.3)	0.008	5319	1118 (21.0)	12 474	1994 (16.0)	<0.001

Abbreviations: ACR, albumin:creatinine ratio; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; NA, not applicable; NGSP, National Glycohemoglobin Standardization Program; RAS, renin-angiotensin system; SMBG, self-monitoring of blood glucose.

Data are expressed as mean ± SD or median (interquartile range), unless otherwise indicated.

bolus-only, and premixed regimens (Figure 1). Among patients with DKD, premixed regimen was independently associated with lower mean HbA1c (−2.8 mmol/mol [95% CI −4.4, −1.2] or − 0.26% [95% CI −0.40, −0.11]). Younger age, female sex, long disease duration, low eGFR, low baseline HbA1c, history of CVD, and non-use of oral glucose-lowering drugs were associated with increased odds of self-reported hypoglycaemia (Table S4). After adjusting for these covariables and using basal-only regimen as reference, the aORs for hypoglycaemia were 1.88 (95% CI 1.58, 2.23) and 1.65 (95% CI 1.45, 1.88) for basal-bolus and premixed regimens, respectively (Figure 2).

Compared to those without DKD, premixed insulin users with DKD had a lower mean HbA1c (−2.4 mmol/mol [95% CI −3.6, −1.2] vs. −0.3 mmol/mol [95% CI −1.3, 0.8] or − 0.22% [95% CI −0.33, −0.11] vs. −0.03% [95% CI −0.12, 0.07]; $P_{interaction}$ = 0.012 [Figure 3A]), but increased odds of self-reported hypoglycaemia (aOR 1.81 [95% CI 1.54, 2.13] vs. 1.34 [95% CI 1.16, 1.54]; $P_{interaction}$ < 0.001 [Figure 3B]). Among patients treated with a basal-bolus regimen, women (aOR 1.92 [95% CI 1.52, 2.41] vs. 1.60 [95% CI 1.29, 1.98] in men; $P_{interaction}$ = 0.758) and patients with YOD (aOR 2.18 [95% CI 1.70, 2.77] vs. 1.80 [95% CI 1.46, 2.20] in those with late-onset diabetes; $P_{interaction}$ = 0.263) showed a similar direction of increased odds of self-reported hypoglycaemia, albeit not statistically significant (Figure 3B).

4 | DISCUSSION

In this JADE Register with detailed information of 97 852 patients with type 2 diabetes recruited from 11 countries/regions in Asia,

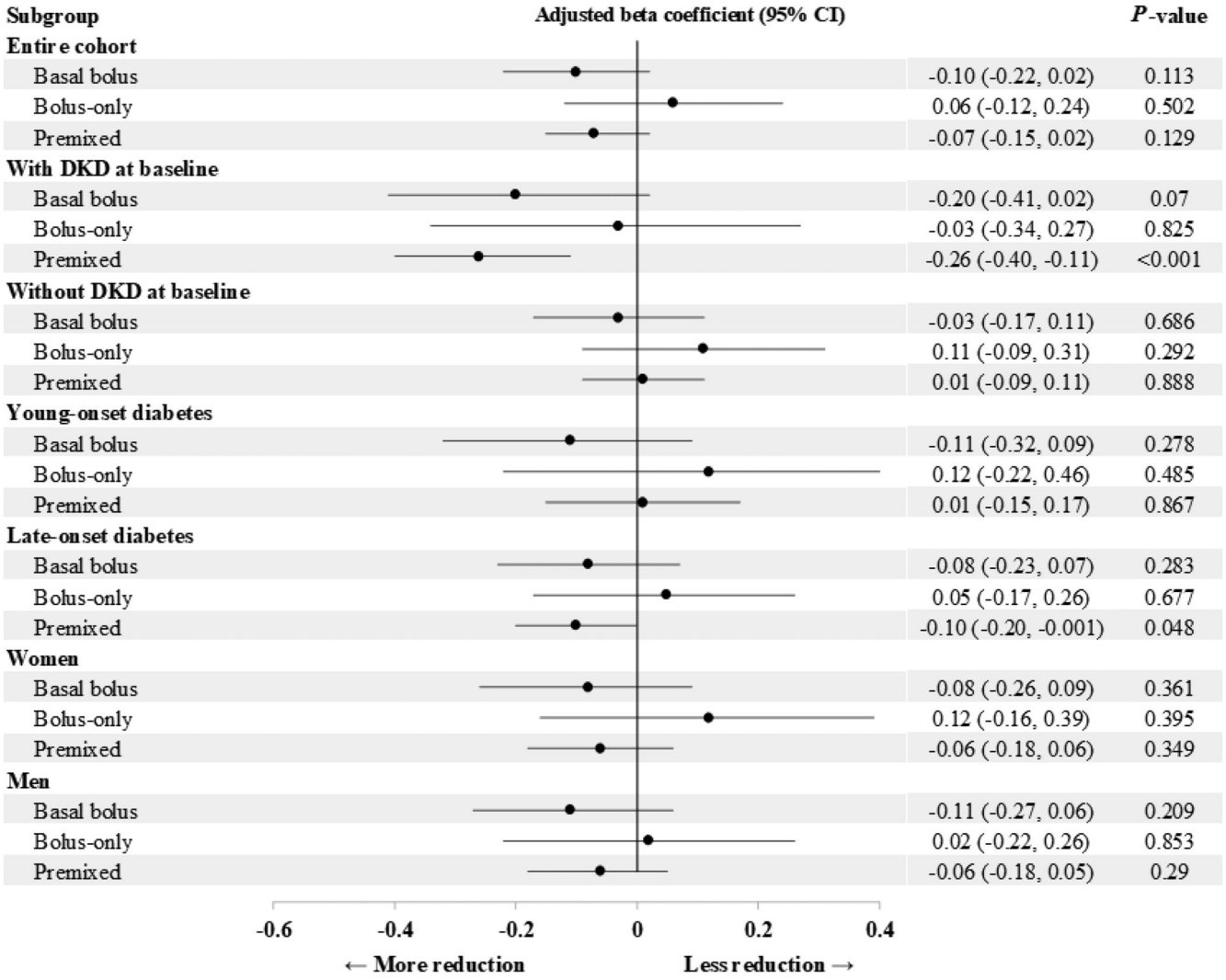

FIGURE 1 Multivariable linear regression analyses of the associations between different insulin regimens and mean glycated haemoglobin (HbA1c) at baseline using basal-only regimen as the reference, stratified by gender, young-onset diabetes (YOD), and diabetic kidney disease (DKD) at baseline. HbA1c reporting was based on the National Glycohemoglobin Standardization Program (NGSP) unit. The linear regression analyses were adjusted for age, sex, duration of diabetes, country/region, estimated glomerular filtration rate (eGFR), logarithmically transformed weight-adjusted total daily insulin dose, use of oral glucose-lowering drugs at baseline, and history of cardiovascular disease, as appropriate. Patients with YOD were defined as those with a diagnosis of diabetes before the age of 40 years. DKD was defined as eGFR<60 mL/min/1.73m^2. CI, confidence interval

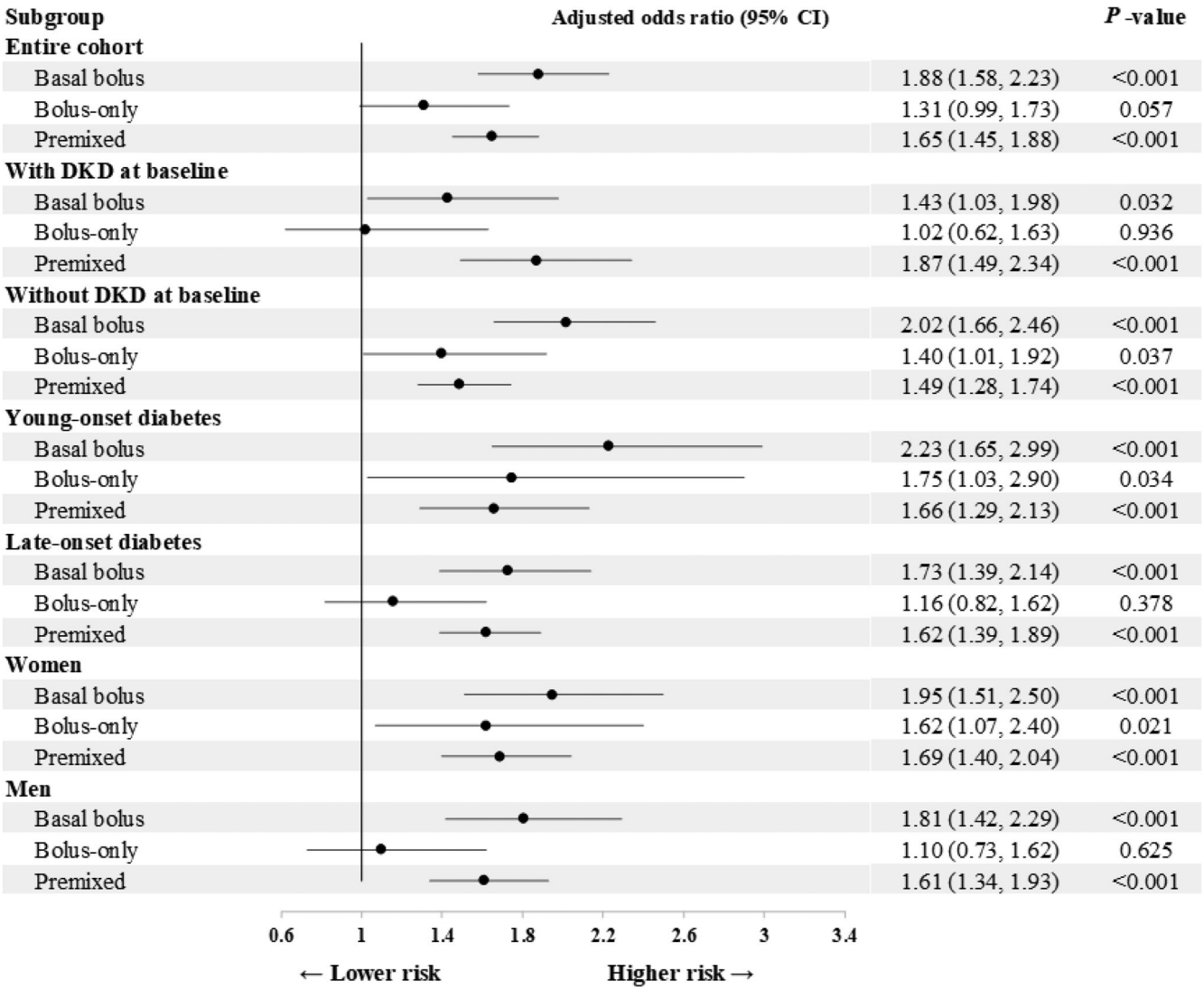

FIGURE 2 Multivariable logistic regression analyses of the associations between different insulin regimens and self-reported hypoglycaemia using basal-only regimen as the reference, stratified by gender, young-onset diabetes (YOD), and diabetic kidney disease (DKD) at baseline. The logistic regression analyses were adjusted for age, sex, duration of diabetes, country/region, glycated haemoglobin (HbA1c; NGSP, %), estimated glomerular filtration rate (eGFR), logarithmically transformed weight-adjusted total daily insulin dose, use of oral glucose-lowering drugs at baseline, and history of cardiovascular disease, as appropriate. Patients with YOD were defined as those with a diagnosis of diabetes before the age of 40 years. CI, confidence interval. DKD was defined as eGFR <60 mL/min/1.73m^2. CI, confidence interval; NGSP, National Glycohemoglobin Standardization Program

one in five patients was treated with insulin with different regimens in different countries. Despite the use of similar or higher insulin dosage (0.3–0.8 units/kg) than that reported in clinical trials, only 17% of these patients achieved an HbA1c level < 53 mmol/mol (7%). Overall, nearly one in five patients reported hypoglycaemia, especially among patients with YOD, women, or those with DKD treated with premixed regimen, after adjusting for confounders. While clinical trials have confirmed the efficacy of multiple medications including insulin therapy in controlled settings, their effectiveness in real-world practice depends on many factors such as access, adherence, and support systems.

In the UK Prospective Diabetes Study (UKPDS), modelling data demonstrated that type 2 diabetes is a progressive disease with 50% loss of pancreatic β-cell function at diagnosis, which continues to decrease regardless of therapy with diet, sulphonylureas, or metformin.[21] Between 1995 and 2007, the US Behavioural Risk Factor Surveillance System reported that 22% of adults aged ≥40 years with type 2 diabetes required insulin therapy.[22] Notably, Asian people are more likely to have renal and β-cell dysfunction and thus, may require insulin therapy earlier than white people to achieve glycaemic control.[14,23,24] Apart from high HbA1c and BMI (by Asian criteria), the present cohort had relatively good control of other cardiometabolic risk factors, with nearly half of them treated with organ-protective drugs and > 80% of them performing self-monitoring of blood glucose.

Achieving glycaemic and weight control is challenging, especially in those treated with complex insulin regimens which demand high

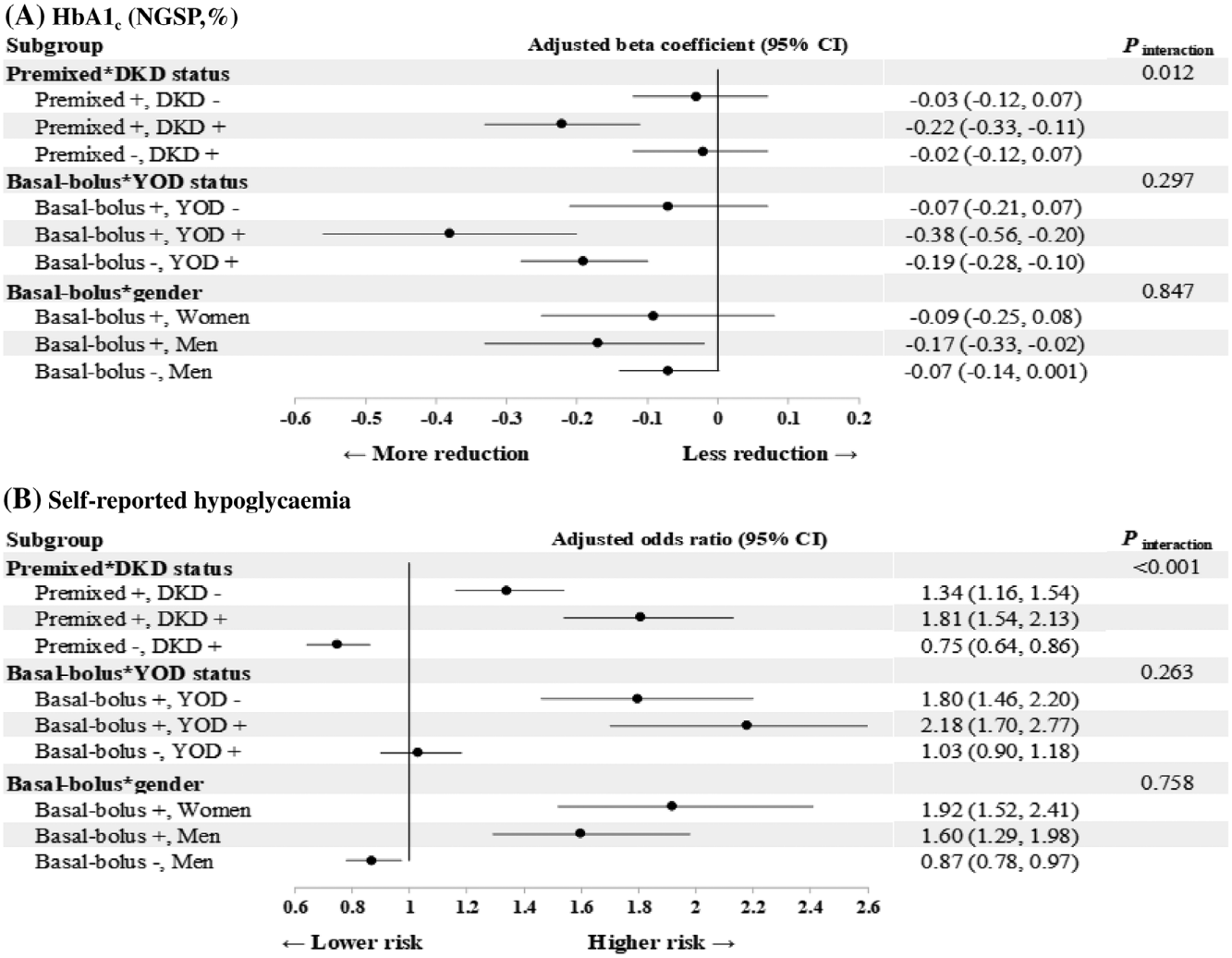

FIGURE 3 Modifying effects of gender, young-onset diabetes (YOD), and diabetic kidney disease (DKD) at baseline on the impact of intensive insulin regimens in the entire cohort

For each subgroup, the respective reference groups were: premixed - DKD -; basal-bolus -, YOD -; and basal-bolus -, women. Based on the results from Tables S5 to S8, we included each relevant cross-product item in the linear and logistic regression analyses of the entire cohort, adjusting for age, sex, duration of diabetes, country/region, estimated glomerular filtration rate (eGFR), logarithmically transformed weight-adjusted total daily insulin dose, use of oral glucose-lowering drugs at baseline, and history of cardiovascular disease, as appropriate. For self-reported hypoglycaemia, we also adjusted for glycated haemoglobin (HbA1c) at baseline. Patients with YOD were defined as those with a diagnosis of diabetes before the age of 40 years. DKD was defined as eGFR <60 ml/min/1.73m^2. CI, confidence interval; NGSP, National Glycohemoglobin Standardization Program

levels of patient participation and self-management. In a global real-world survey, 11% to 13% of insulin-treated patients with either type 1 or type 2 diabetes admitted to having discontinued their insulin intermittently for 1 to 2 months in the past for multiple reasons, including lack of education and support.[25] This real-world evidence points to the importance of patient education and engagement, calling for better psychosocial and behavioural support from the healthcare team (including clinicians and allied health personnel), families, and peers to optimize diabetes care.[18,26]

In this real-world register, which involved mainly hospital-based clinics, premixed and basal-only regimens were most popular, although basal-bolus regimen was also often used in Indonesia and Malaysia. The latest American Diabetes Association/European Association for the Study of Diabetes guidelines emphasize individualized treatment goals and strategies, and that if HbA1c goal is not attained despite the use of multiple oral drugs, glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a possible option.[19] That said, because of the high cost of GLP-1RAs, initiation of basal insulin, followed by addition of prandial insulin before the largest meal or switching to twice- or thrice-daily premixed insulin, remains the mainstream therapy.[19] We reported that only 10% of patients were treated with a basal-bolus regimen, probably for reasons of patients' acceptability to multiple injections, patients' fear of hypoglycaemia, lack of support systems, and high treatment costs, especially if the treatment is paid out-of-pocket.[27-29] The high treatment cost is in part due to the complexity of pricing, procurement, and supply chain of insulin.[28]

Despite having lower HbA_{1c} overall, more patients with DKD treated with premixed insulin reported hypoglycaemia than those without DKD. We and others have reported that DKD is a major risk factor for hypoglycaemia due to multiple factors including reduced renal gluconeogenesis and drug clearance.[30,31] Although we did not record the year of insulin initiation in these patients, patients with DKD had over 10 years of diabetes when the use of insulin analogues and basal-bolus regimen were less popular.[32,33]

In this real-world register, more women reported hypoglycaemia than men, after adjusting for confounders. Despite having similar glycaemic control (mean HbA1c 72 mmol/mol [8.7%]), women had a higher BMI by 0.4 kg/m^2 and a higher weight-adjusted TDD for any insulin regimen compared to men. In a previous analysis, depression was more common in Chinese women than men, with depression being associated with both hypoglycaemia and hyperglycaemia; this was attenuated after adjustment for self-report of non-adherence.[34,35] Although we did not document these psychosocial and behavioural factors in this survey, healthcare providers should be aware of these factors which may be linked to non-adherence. Indeed, the high weight-adjusted TDD in women and patients with YOD and, to some extent, those of DKD, irrespective of insulin regimens, raised the possibility of suboptimal treatment adherence. Increasing insulin dosage without taking into consideration other factors that can influence glycaemic control (eg, lifestyles, diets, work schedule, emotions) can lead to a cycle of weight gain, insulin resistance, glycaemic variability, and non-adherence, which will increase the complexity of management.[27] As such, the use of team-based care to perform periodic assessment to stratify risk, provide self-management support, and enhance patient–provider communication may help optimize care.[26]

In this survey, 4% of patients were treated with bolus-only regimen, although this is not routinely recommended.[19] In a pooled analysis of randomized clinical trials involving patients with suboptimally controlled type 2 diabetes treated with oral glucose-lowering drugs, Asian people had lower fasting plasma glucose but higher HbA1c levels than white people, despite a similar dosage of basal insulin.[36] These findings lent support to the reduced capacity of Asian people to overcome high postprandial glucose excursions, which require additional treatment.[24] In this insulin-treated cohort, 25% of patients had YOD. While 17% of the entire cohort attained HbA1c <53 mmol/mol (7%), only 14% of patients with YOD attained goal, compared to 18% in their late-onset peers. Although more patients with YOD were put on basal-bolus and premixed regimens with higher weight-adjusted TDD than their late-onset peers, they had worse glycaemic control, raising the possibility of non-adherence and suboptimal self-care.

To our knowledge, this is the first and largest real-world type 2 diabetes register using the same protocol for data collection which allows robust comparisons among different care settings. In this analysis, we have demonstrated the different patterns of insulin regimens in Asia where data are relatively scarce. We further identified different quality of glycaemic control with different insulin regimens, which was influenced by gender, YOD, and DKD status, after adjusting for covariables and variances due to countries/regions in our regression analyses.

There are several study limitations. First, despite the proven efficacy of insulin treatment in clinical trial settings, fewer than 20% of patients achieved glycaemic goals in this real-world register. However, we could not assess the impacts of healthcare settings (notably reimbursement and healthcare coverage), physicians' practice behaviours (including knowledge and skills on insulin initiation and intensification), insulin access and affordability, as well as patients' psychosocial–behavioural attributes on these care gaps. Second, the hypoglycaemia assessment in the JADE Register did not capture data on nocturnal hypoglycaemia, or adjustments of insulin dosages and/or regimens during Ramadan fasting. In view of different clinical needs in this special population,[37] a separate study that focuses on the effects of Ramadan fasting is warranted. Third, given that the present study aimed to quantify the impacts of different types of insulin regimens on glycaemic control, we did not compare the effects of human vs analogue insulin. However, existing evidence has consistently reported a similar efficacy in HbA1c reduction, but with a lower risk of hypoglycaemia with the use of analogues insulin compared to human insulin.[29] Last, we acknowledge limitations inherent in cross-sectional surveys that precluded causal inference.

In conclusion, using real-world evidence from the JADE Register, we found that premixed and basal-only regimens were most commonly used by Asian people with type 2 diabetes. While more patients with DKD reported hypoglycaemia, especially those treated with premixed regimen, the low use of basal-bolus regimen and a consistent pattern of poor glycaemic control despite optimal dosage of insulin, call for a better supporting system at patient, provider, organization, and system levels.

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CONFLICTS OF INTEREST

J.C.N.C. is the Chief Executive Officer (on a pro-bono basis) of Asia Diabetes Foundation, a charitable foundation established under the Chinese University of Hong Kong Foundation for developing the JADE Technology. J.C.N.C. has received research grants and/or honoraria for consultancy or giving lectures, from AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly, GlaxoSmithKline, Merck Serono, Merck Sharp & Dohme, Novo Nordisk, Pfizer, and Sanofi. A.P.S.K. has received research grants and/or speaker honoraria from Abbott, Astra Zeneca, Eli Lilly, Merck Serono, Nestle, and Novo Nordisk. The proceeds have been donated to the Chinese University of Hong Kong, American Diabetes Association, and other charity organizations to support diabetes research and education. J.K. has received speaker honoraria from AstraZeneca, Boehringer Ingelheim, Medtronic, Novo Nordisk, and Sanofi. L.L.L. has received research grants and/or speaker honoraria from AstraZeneca, Boehringer Ingelheim, Medtronic, Merck Serono, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Procter & Gamble Health, Sanofi, and Servier. T.L., K.W., K.K., and T.T. are employees and

stockholders of Eli Lilly and Company. Other authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

J.C.N.C. and A.P.S.K. conceptualized the work. A.P.S.K., L.L.L., J.K., W.J., W.H.S., L.S., A.T., K.N.T., K.Y. and J.C.N.C. were involved in the patient recruitment. E.S.H.L. and L.L.L. performed the analysis with support from J.C.N.C. A.P.S.K. wrote the first draft and J.C.N.C. finalized the manuscript. All authors participated in the research methodology, data interpretation, manuscript revision for important intellectual content, and approved the final version of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. J.C.N.C. is the guarantor of this work and, as such, has full access to all the data in the study and takes full responsibility for the integrity and accuracy of the data.

DATA AVAILABILITY

Data cannot be shared publicly as we did not have patients' consent to release the data in the public domain for open, unrestricted access. Researchers who are interested and meet the criteria for research access to our data may apply for data access via Asia Diabetes Foundation (enquiry@adf.org.hk).

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SUPPORTING INFORMATION

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

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