New Diabetes Diagnostic Threshold of Hemoglobin A_{1c} and the 3-Year Incidence of Retinopathy

Yusuke Tsugawa,[1] Osamu Takahashi,[2] James B. Meigs,[3] Roger B. Davis,[1,4] Fumiaki Imamura,[5] Tsuguya Fukui,[2] William C. Taylor,[1] and Christina C. Wee[1]

The new diagnostic threshold of hemoglobin A_{1c} was made based on evidence from cross-sectional studies, and no longitudinal study supports its validity. To examine whether hemoglobin A_{1c} of 6.5% or higher defines a threshold for elevated risk of incident retinopathy, we analyzed longitudinal data of 19,897 Japanese adults who underwent a health checkup in 2006 and were followed-up 3 years later. We used logistic regression models and restricted cubic spline models to examine the relationship between baseline hemoglobin A_{1c} levels and the prevalence and the 3-year incidence of retinopathy. The restricted cubic spline model indicated a possible threshold for the risk of incident retinopathy at hemoglobin A_{1c} levels of 6.0–7.0%. Logistic regression analysis found that individuals with hemoglobin A_{1c} levels of 6.5–6.9% were at significantly higher risk of developing retinopathy at 3 years compared with those with hemoglobin A_{1c} levels of 5.0–5.4% (adjusted odds ratio, 2.35 [95% CI 1.08–5.11]). Those with hemoglobin A_{1c} levels between 5.5 and 6.4% exhibited no evidence of elevated risks. We did not observe a threshold in the analysis of prevalent retinopathy. Our longitudinal results support the validity of the new hemoglobin A_{1c} threshold of 6.5% or higher for diagnosing diabetes.

Diabetes is an increasingly important global public health concern (1). An estimated 285 million people, or 6.4% of the world's population, lived with diabetes in 2010, and the number is expected to grow to 438 million by 2030 (1). In the U.S., 8.3% of children and adults are living with diabetes (2); likewise, in Japan, 7.8% of the population has diabetes (3).

Recently, the International Expert Committee suggested use of a hemoglobin A_{1c} (HbA_{1c}) level of 6.5% or higher as the threshold for diagnosing diabetes (4,5). This criterion was subsequently adopted by the American Diabetes Association, European Association for the Study of Diabetes, and World Health Organization (4,5). In making its decision, the expert panel was informed by evidence from several cross-sectional studies that showed the association between HbA_{1c} level and the prevalence of retinopathy (4–12). The outcome of retinopathy has been historically accepted as the best criterion for comparing glycemic measures among several complications of diabetes (13,5), because it is a specific complication of diabetes that can be measured objectively (13,14). Few longitudinal studies have examined the association between HbA_{1c} levels and the risk of retinopathy in the general population, and these studies do not support the validity of this new diagnostic threshold (6,15–17). Many of the previous studies did not adjust for independent risk factors and confounders for retinopathy, such as age and hypertension.

To examine the validity of the new HbA_{1c} thresholds, we tested the hypothesis that HbA_{1c} level of 6.5% or higher would define a threshold for increased 3-year incidence of retinopathy in a large cohort of Japanese adults.

RESEARCH DESIGN AND METHODS

Participants and setting. We analyzed data from a cohort of 21,137 Japanese adults aged ≥21 years who underwent a health checkup between January 1 and 31 December 2006 and were followed-up 3 years later at the Center for Preventive Medicine, St. Luke's International Hospital (Tokyo, Japan). We used 3-year incidence of retinopathy as the outcome measure in our study based on evidence that retinopathy develops within 5 years of diagnosis of diabetes in substantial proportion of people with diabetes (18). The participants underwent self-administered clinical surveys (e.g., use of the diabetes medication, diagnosis of diabetes, family history of diabetes, smoking status, alcohol consumption), physical examination, laboratory testing, imaging studies, and retinal photographs.

For analysis of prevalent retinopathy, we excluded individuals without information on baseline HbA_{1c} (n = 375), those who did not undergo baseline retinal exams (n = 303), and those with ungradable retinal images (n = 26), resulting in a sample size of 20,433. For our longitudinal analysis of incident retinopathy, we further excluded those with retinopathy at baseline (n = 245), those missing information on follow-up retinal exams (n = 223), and those with ungradable photographs at follow-up visits (n = 68), resulting in a final sample size of 19,897. Institutional review board approvals were obtained from Beth Israel Deaconess Medical Center (Boston, MA) and St. Luke's International Hospital (Tokyo, Japan).

Retinopathy. Retinal digital photos were taken for both eyes for the participants at both baseline and follow-up visits. The Canon CR-DG10 digital camera (Canon, Tokyo, Japan) was used to take one digital image per eye (total two images per participant) through a nonpharmacologically dilated pupil. Participants were tested in a dark room to allow the pupils to dilate naturally in preparation for the retinal imaging examination. After dark adaptation, 45° retinal photographs centered on the macula were taken of both eyes. The digital images were graded by trained ophthalmologists. Retinopathy was defined as the presence of hard exudates, cotton wool spots, retinal hemorrhage, or more severe forms of retinopathy, the Fukuda standard (19) A2 or higher.

HbA_{1c}. Whole-blood samples collected from the participants were assayed for HbA_{1c} immediately after the they were obtained with high-performance liquid chromatography (Tosoh G7; Tosoh Corporation, Tokyo, Japan). We categorized HbA_{1c} levels as follows: <5.0, 5.0–5.4, 5.5–5.9, 6.0–6.4, 6.5–6.9, and ≥7.0%. Those with HbA_{1c} levels of 5.0–5.4% comprised the largest sample and were used as the reference category in our logistic regression models.

Other clinical variables of interest. We also extracted the potential predictors of retinopathy in those with diabetes: age (20), systolic and diastolic blood pressures (21–26), LDL cholesterol (27), HDL cholesterol, triglycerides (27,28), BMI, self-reported family history of diabetes, smoking status (29,30), and alcohol consumption (31). Triglyceride levels were right-skewed; therefore, we used a logarithmic transformation of the variable to improve the fit for the model. The diagnosis of diabetes was defined on based on self-report of

From the [1]Division of General Medicine and Primary Care, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts; the [2]Division of General Internal Medicine, St. Luke's International Hospital, Tokyo, Japan; the [3]General Internal Medicine Unit, Massachusetts General Hospital, Boston, Massachusetts; the [4]Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts; and the [5]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts.
Corresponding author: Yusuke Tsugawa, ytsugawa@bidmc.harvard.edu.
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a diagnosis of diabetes or of taking medication for diabetes. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or the use of hypertension medication. All variables, including HbA_{1c} and retinal images, were measured and recorded both at baseline and at follow-up visits.

Statistical analysis. We constructed a series of logistic regression models to investigate the association between HbA_{1c} levels and the risk of retinopathy. Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, hypertension, diagnosis of diabetes, HDL and LDL cholesterol, log-transformed triglyceride, BMI (<25, 25.0–29.9, or ≥30 kg/m^2), alcohol consumption (regular, occasional, or never drinker), smoking status (current, former, or never smoker), and family history of diabetes (yes or no). We evaluated these models to estimate multivariable-adjusted odds ratios (ORs) and 95% CIs for prevalent retinopathy (models 1a and 2a) and incident retinopathy (models 1b and 2b). To examine the impact of integrating known cases of diabetes in our analysis, we excluded those with a diagnosis of diabetes and developed additional models 3a and 3b, in which we adjusted for all the variables in models 2, with the exception of the diagnosis of diabetes.

To assess whether the threshold where the risk begins to increase (inflection point exists), we examined the continuous associations between HbA_{1c} level and the prevalence or the incidence of retinopathy without assuming linearity by fitting restricted cubic spline models (32–33) with the knots corresponding to the HbA_{1c} cutoff points of interest: 5.0, 5.5, 6.0, 6.5, 7.0, and 7.5%. The ORs were adjusted for all the variables included in model 2. All statistical analyses were conducted with SAS statistical software version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Study participants. Table 1 shows the baseline characteristics of the study population overall and according to HbA_{1c} levels. Approximately 49% were men. The mean age was 51.0 years, the mean HbA_{1c} was 5.6%, and the mean (±SD) follow-up period was 3.0 ± 0.29 years. Participants with higher HbA_{1c} levels were more likely to be older, to be men, to smoke, to take medication for hypertension, and to have several clinical risk factors, including elevated blood pressure, higher BMI, lower HDL cholesterol, higher triglyceride, and a family history of diabetes.

Prevalence of retinopathy. Among the 20,433 participants, the crude prevalence of retinopathy was 1.2% (245/20,433). The adjusted ORs and 95% CIs for prevalent retinopathy are shown in Table 2. After initial adjustment for age and sex (model 1a), the prevalence of retinopathy was significantly higher at HbA_{1c} levels ≥6.5% than in the reference category. After further adjustments (model 2a), this estimate was attenuated, and only HbA_{1c} levels ≥7.0% achieved statistical significance.

Cumulative incidence of retinopathy. The crude cumulative incidence of retinopathy at 3 years was 0.85%

TABLE 1
Baseline characteristics of study participants according to the HbA_{1c} value at baseline

	HbA_{1c} categories						
	Overall	<5.0%	5.0–5.4%	5.5–5.9%	6.0–6.4%	6.5–6.9%	≥7.0%
Sample size	20,433	1,719	9,300	6,376	2,046	416	576
Baseline HbA_{1c} (%)*	5.6 ± 0.6	4.9 ± 0.2	5.3 ± 0.1	5.7 ± 0.1	6.1 ± 0.1	6.7 ± 0.1	8.0 ± 1.1
Follow-up HbA_{1c}(%)*	5.7 ± 0.5	5.1 ± 0.3	5.5 ± 0.2	5.8 ± 0.2	6.1 ± 0.4	6.8 ± 0.7	7.5 ± 1.1
Fasting blood glucose (mg/dL)*	100.6 ± 15.3	93.4 ± 7.2	96.2 ± 7.7	100.2 ± 8.5	107.0 ± 11.4	123.1 ± 15.5	157.5 ± 39.7
Age (years)*	51.0 ± 11.7	43.0 ± 9.5	47.9 ± 10.9	53.9 ± 11.0	58.6 ± 10.3	60.5 ± 9.7	60.7 ± 10.2
Sex (female) (%)	50.9	58.9	52.7	50.9	48.0	28.9	26.0
Systolic blood pressure (mmHg)*	119.0 ± 17.6	113.7 ± 16.0	116.4 ± 16.7	120.6 ± 17.9	124.8 ± 17.8	128.1 ± 18.5	130.9 ± 18.0
Diastolic blood pressure (mmHg)*	73.9 ± 11.3	70.4 ± 10.5	72.5 ± 10.9	75.1 ± 11.3	77.2 ± 11.2	78.9 ± 11.0	80.3 ± 10.9
BMI (%)†							
≤24.9	80.0	89.3	84.6	77.9	69.6	54.6	57.6
25–29.9	17.8	10.0	14.1	20.0	26.3	35.1	33.9
≥30	2.2	0.8	1.3	2.2	4.1	10.3	8.5
Diagnosis of diabetes (%)‡	5.3	1.6	1.4	2.8	7.5	35.3	77.3
Hypertensive treatment (%)	10.5	4.0	6.8	12.0	19.5	29.8	28.1
Family history of diabetes (%)	12.3	11.4	11.2	11.9	15.9	17.8	21.0
Fasting LDL cholesterol (mg/dL)*	119.6 ± 29.9	103.6 ± 26.9	115.7 ± 28.9	125.5 ± 29.8	129.6 ± 29.2	124.5 ± 29.5	127.1 ± 29.8
Fasting HDL cholesterol (mg/dL)*	64.0 ± 16.0	66.8 ± 16.1	65.2 ± 15.7	63.5 ± 16.1	61.2 ± 16.2	56.7 ± 15.2	55.6 ± 14.4
Triglycerides (mg/dL)							
Median	83	67	76	88	102	112	120
Interquartile range	59–122	49–96	55–111	63–130	71–147	77–163	78–174
Serum creatinine (mg/dL)							
Median	0.77	0.73	0.76	0.77	0.78	0.83	0.83
Interquartile range	0.66–0.90	0.64–0.87	0.65–0.89	0.66–0.91	0.67–0.92	0.71–0.94	0.71–0.92
Hemoglobin (g/dL)*	13.6 ± 2.0	13.6 ± 1.7	13.6 ± 1.8	13.4 ± 2.2	13.4 ± 2.4	13.8 ± 2.0	14.2 ± 1.6
Alcohol use (%)							
Regular drinker	43.6	51.4	46.2	40.2	37.2	42.2	38.0
Occasional drinker	18.0	19.2	18.8	17.7	15.2	14.3	17.4
Never	38.5	29.4	35.0	42.2	47.6	43.4	44.6
Smoking status (%)							
Current smoker	14.2	13.9	13.4	14.2	15.1	18.9	20.3
Former smoker	25.0	21.8	23.6	25.7	26.5	36.5	35.1
Never smoked	60.8	64.3	63.0	60.1	58.4	44.6	44.6

*Mean ± SD. †BMI is the weight in kilograms divided by the square of the height in meters. ‡Self-reported diagnosis of diabetes or taking medication for diabetes.

TABLE 2
Adjusted ORs and 95% CIs for the prevalence of retinopathy across different baseline HbA_{1c} levels

	Individuals with and without diabetes								Individuals with no diabetes				
			Model 1a*			Model 2a†					Model 3a‡		
HbA_{1c} (%)	*N*	No. of cases (%)	OR	95% CI	*P*	OR	95% CI	*P*	*N*	No. of cases (%)	OR	95% CI	*P*
<5.0	1,719	10 (0.6)	1.17	0.60–2.29	0.65	1.08	0.55–2.12	0.83	1,692	10 (0.6)	1.20	0.61–2.36	0.60
5.0–5.4	9,300	67 (0.7)	1.00	Ref.	Ref.	1.00	Ref.	Ref.	9,170	65 (0.7)	1.00	Ref.	Ref.
5.5–5.9	6,376	76 (1.2)	1.14	0.81–1.59	0.46	1.16	0.82–1.63	0.40	6,198	72 (1.2)	1.12	0.79–1.58	0.54
6.0–6.4	2,046	26 (1.3)	0.91	0.57–1.46	0.71	0.88	0.54–1.42	0.59	1,893	21 (1.1)	0.80	0.48–1.34	0.39
6.5–6.9	416	17 (4.1)	**2.63**	**1.50–4.59**	**0.0007**	1.81	0.98–3.37	0.060	268	5 (1.9)	1.18	0.46–3.03	0.73
≥7.0	576	49 (8.5)	**5.69**	**3.82–8.47**	**<0.0001**	**3.02**	**1.71–5.34**	**0.0001**	130	5 (3.9)	**3.00**	**1.14–7.84**	**0.026**

Statistically significant results at $P < 0.05$ are indicated in boldface. *Adjusted for age and sex. †Adjusted for age, sex, hypertension, diagnosis of diabetes, HDL and LDL cholesterol, log-transformed triglyceride, BMI, alcohol consumption, smoking status, and family history of diabetes. ‡Adjusted for all the variables in model 2a, with the exception of the diagnosis of diabetes.

(170/19,897). After initial adjustment for age and sex, there was no significant association between HbA_{1c} value and the incidence of retinopathy at HbA_{1c} <6.5%; compared with the reference category, however, HbA_{1c} levels of 6.5–6.9% were associated with significantly higher risk of developing retinopathy at 3 years (OR 2.35 [95% CI 1.08–5.11]; $P = 0.031$) (Table 3). The risk remained significantly higher after further adjusting for the confounders and other independent risk factors for retinopathy (model 2b). Our results did not alter substantially after the exclusion of those with diagnosis of diabetes at baseline in model 3b.

In our analysis to evaluate whether the relationship between baseline HbA_{1c} levels and prevalence of retinopathy is nonlinear, we found that the nonlinear relationship was borderline significant (P for curve = 0.08) (Fig. 1). For the outcome of incident retinopathy, however, the nonlinear relationship was statistically significant ($P = 0.001$), suggesting a possible threshold at HbA_{1c} levels between 6.0 and 7.0%. We observed a dose-response relationship between higher HbA_{1c} levels and increased risk of incident retinopathy at HbA_{1c} ≥6.5%. The restricted cubic spline analysis for the nondiabetic subpopulation yielded similar findings (data not shown).

DISCUSSION

We found that Japanese adults with HbA_{1c} levels of 6.5–6.9% were at significantly higher risk of developing retinopathy at 3 years than were those with HbA_{1c} levels of 5.0–5.4%, whereas the risks did not increase among those with HbA_{1c} levels <6.5%. To the best of our knowledge, this is the first longitudinal study supporting the validity of the new diagnostic threshold of HbA_{1c} recommended by the International Expert Committee (5,11). In contrast, we did not observe an explicit threshold effect of HbA_{1c} in the analyses of the prevalent retinopathy.

Although there have been several longitudinal studies examining the association between HbA_{1c} levels and the risk of retinopathy, most of those studies were limited to samples treated for diabetes (29,34–38). There have been only a few small longitudinal studies of general nondiabetic populations (6,15–17). Possibly because of small sample sizes, results from these previous studies did not support the current HbA_{1c} threshold for diagnosing diabetes (6,15–17). In the Pima Indian study ($N = 927$), investigators found that the risk of incident retinopathy begin to increase only at HbA_1 levels of 9.1% (6). Only HbA_1 data were available at that time (HbA_{1c} measurements were unavailable), and no adjustments were made for hypertension and other independent risk factors for retinopathy in that study (6). The longitudinal study ($N = 233$) by van Leiden et al. (15) found that the risk of developing retinopathy was significantly higher in the highest tertile of HbA_{1c} (HbA_{1c} 5.8–13.1%) relative to the lowest tertile (HbA_{1c} 4.3–5.2%). Because of small sample size, these investigators collapsed HbA_{1c} levels from 5.8 to 13.1% into a single category. Selvin et al. (16) examined the risk of retinopathy among participants from the Atherosclerosis Risk in Communities study. The overall sample size of this study was large ($N = 11,357$), but repeated retinal examinations were performed on only 767 people. These investigators were unable to detect a statistically

TABLE 3
Adjusted ORs for developing new retinopathy at 3 years across different baseline HbA_{1c} levels

	Individuals with and without diabetes								Individuals with no diabetes				
			Model 1b*			Model 2b†					Model 3b‡		
HbA_{1c} (%)	*N*	No. of cases (%)	OR	95% CI	*P*	OR	95% CI	*P*	*N*	No. of cases (%)	OR	95% CI	*P*
<5.0	1,696	8 (0.5)	1.05	0.49–2.21	0.91	0.97	0.46–2.06	0.93	1,669	8 (0.5)	1.03	0.48–2.19	0.94
5.0–5.4	9,142	54 (0.6)	1.00	Ref.	Ref.	1.00	Ref.	Ref.	9,016	53 (0.6)	1.00	Ref.	Ref.
5.5–5.9	6,202	51 (0.8)	1.04	0.70–1.54	0.85	1.09	0.73–1.62	0.67	6,030	49 (0.8)	1.04	0.70–1.56	0.83
6.0–6.4	1,970	18 (0.9)	0.93	0.54–1.61	0.79	1.00	0.57–1.76	1.00	1,825	17 (0.9)	0.97	0.55–1.73	0.93
6.5–6.9	388	9 (2.3)	**2.24**	**1.08–4.65**	**0.031**	**2.35**	**1.08–5.11**	**0.031**	257	6 (2.3)	**2.46**	**1.01–5.97**	**0.047**
≥7.0	499	30 (6.0)	**5.93**	**3.65–9.62**	**<0.0001**	**6.45**	**3.21–12.93**	**<0.0001**	117	5 (4.3)	**5.52**	**2.07–14.74**	**0.0006**

Statistically significant results at $P < 0.05$ are indicated in boldface. *Adjusted for age and sex. †Adjusted for age, sex, hypertension, diagnosis of diabetes, HDL and LDL cholesterol, log-transformed triglyceride, BMI, alcohol consumption, smoking status, and family history of diabetes. ‡Adjusted for all the variables in model 2b, with the exception of the diagnosis of diabetes.

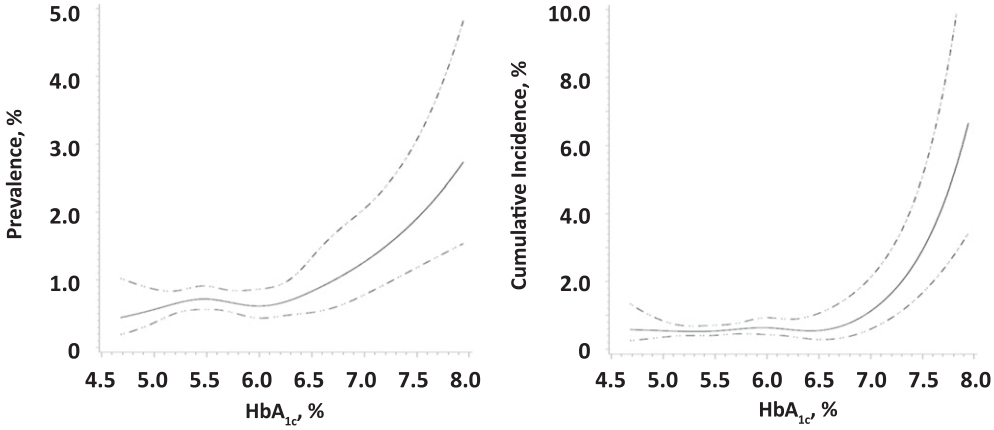

FIG. 1. Associations between baseline HbA_{1c} levels and the prevalence (*A*) or cumulative incidence (*B*) of retinopathy . Multivariable-adjusted logistic regression models with restricted cubic spline were used: left for prevalence (*N* = 20,433) and right for 3-year cumulative incidence (*N* = 19,897). The solid lines present adjusted ORs of restricted cubic spline model with six knots specified at HbA_{1c} levels of 5.0, 5.5, 6.0, 6.5, 7.0, and 7.5%. The dashed lines show the 95% CI from the restricted cubic spline model. HbA_{1c} levels were truncated at the 1st and 99th percentiles (4.7 and 7.9%, respectively). The predicted prevalence and cumulative incidence were adjusted for age, sex, hypertension, diagnosis of diabetes, HDL and LDL cholesterol, log-transformed triglyceride levels, BMI, family history of diabetes, alcohol use, and smoking status.

significant threshold in the association of HbA_{1c} with the incidence of retinopathy, possibly because of the lack of power. Recently, Massin et al. (17) studied 700 participants from the Data From an Epidemiological Study on the Insulin Resistance Syndrome study, in which participants were followed up for 10 years, and proposed an HbA_{1c} threshold of 6.0%. Because retinopathy was not evaluated at baseline in this study, however, they were not able to examine the incidence of retinopathy (17).

Our study has several limitations. First, the retinal images were graded in single-field photographs per eye in this study. Multiple photographic fields per eye would have improved the sensitivity of the funduscopic examinations. Second, our study sample was composed exclusively of native Japanese, so whether our results generalize to other populations is unclear. It is noteworthy that in the DETECT-2 project, which pooled studies from the U.S., Australia, India, Japan, and Singapore, they found no racial difference in optimal HbA_{1c} threshold (12). Third, we did not take into account the possible effect of hemoglobinopathies on HbA_{1c} values. However, the prevalence of hemoglobinopathies in Japan is reported to be as low as 0.04% (39) and is therefore likely to have little impact on our overall findings. Finally, the detection of an inflection point in the relation between HbA_{1c} and retinopathy may not in itself establish the optimal threshold for clinicians to use in the diagnosis and treatment of diabetes. The optimal threshold for any patient is the level at which the benefits of diagnosis and treatment exceed harms for that patient. If there were only benefits and no harm in diagnosing and treating diabetes, the inflection point would represent the level of HbA_{1c}. However, when the benefits of diagnosis and treatment of diabetes are small, the optimal diagnostic threshold may be higher than the inflection point we observed.

Our longitudinal study is the first to date to suggest a threshold of risk for incident retinopathy at a 6.5% HbA_{1c} level. These findings support the validity of the new diagnostic HbA_{1c} threshold for diabetes recently adopted by the American Diabetes Association, the European Association for the Study of Diabetes, and the World Health Organization (5,12). Additional longitudinal studies are needed to validate these findings in other populations.

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Y.T., O.T., T.F., W.C.T., and C.C.W. developed the study concept, developed the design, and interpreted the data. Y.T., R.B.D., and F.I. conducted statistical analyses. Y.T., J.B.M., W.C.T., and C.C.W., drafted the manuscript. All the authors revised the manuscript critically for important intellectual content and approved the final manuscript. Y.T. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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