Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

The Role of Triglyceride-Glucose Index in the Prediction of the Development of Hypertension – Findings from a Community Cohort in Singapore

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Abstract

Objectives. Triglyceride-glucose index (TyGI) is an emerging surrogate marker of insulin resistance. We aim to explore the role of triglyceride-glucose index in the prediction of the development of hypertension.

Methodology. We conducted a retrospective cohort study that included 3,183 study participants identified from a community health screening programme who had no baseline hypertension and were then followed up after an average of 1.7 years. Cox proportional-hazard model was used to assess the association between risk of incident hypertension and TyGI in quartiles, while adjusting for demographics and clinical characteristics.

Results. Hypertension occurred in 363 study participants (11.4%). Those who developed hypertension had higher TyGI [8.6 (IQR 8.2-9.0)] than those who did not [8.2 (IQR 8.0-8.7)] (p<0.001). Significant association between TyGI and hypertension was observed in both the unadjusted and proportional hazard model [Quartile (Q)2, p=0.010; Q3, p<0.001 and Q4, p<0.001] and the model that adjusted for demographics (Q2, p=0.016; Q3, p=0.003; Q4, p<0.001). In the model adjusted for clinical covariates, the hazard of developing hypertension remained higher in TyGI Q4 compared to TyGI Q1(Hazard Ratio=2.57; 95% Confidence Interval: 1.71, 3.87). Increasing triglyceride-glucose index accounted for 16.4% of the association between increasing BMI and incident hypertension, after adjusting for age, gender, ethnicity and baseline HDL cholesterol (p<0.001).

Conclusion. Triglyceride-glucose index was an independent predictor of the development of hypertension. It may potentially be used as an inexpensive indicator to predict the development of hypertension and risk-stratify individuals to aid management in clinical practice.

Key words: type 2 diabetes mellitus, triglycerides, hypertension, screening, population science

INTRODUCTION

Hypertension poses a major risk for cardiovascular disease and mortality worldwide.[1-4] It was estimated that 31% of adults had hypertension globally in 2010.[5] As the population ages, the public health burden attributed to hypertension is expected to increase and the need to better understand and control the risk factors associated with the development of hypertension becomes more urgent.

One area of interest is the mounting evidence that shows hypertension and insulin resistance are linked.[4,6,7] However, it is challenging to use hyperinsulinemia-euglycemic clamp, the gold standard for assessing insulin resistance, in routine clinical practice as it is costly, time-consuming and often not readily available.[6,8] In recent years, triglyceride-glucose index (TyGI) has emerged as a promising surrogate of insulin resistance.[9,10] TyGI has been shown to correlate well with hyperinsulinemic-euglycemic clamp and homeostasis model assessment insulin resistance.[11-14]

eISSN 2308-118x (Online)
Printed in the Philippines

Received: June 29, 2022. Accepted: August 27, 2022.
Published online first: January 16, 2023.
https://doi.org/10.15605/jafes.038.01.09

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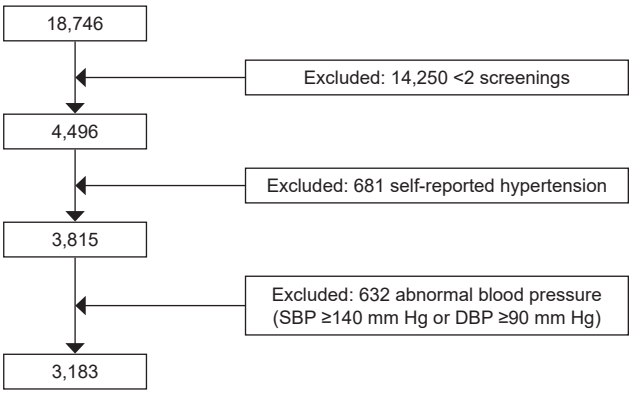
Furthermore, TyGI has been identified as an independent predictor of incident diabetes in a few studies.[8,10,15-17] Two studies in China and Spain also reported that TyGI conferred a higher risk of incident hypertension.[4,18] However, findings are still limited in view of the small number of studies. Interestingly, one study demonstrated interactions of TyGI and obesity on the risk of hypertension in a cross-sectional study.[6] To date, the mechanism on the role of TyGI in development of hypertension is still unclear. As such, we aimed to explore the role of TyGI in the development of hypertension and elucidate its role as a potential mediator in the association between body mass index (BMI) and the development of hypertension. We hypothesized that higher TyGI was linked to higher risk of hypertension, and that TyGI mediated the association between BMI and the development of hypertension.

METHODOLOGY

We conducted a retrospective cohort study on residents who attended the Alexandra Health Community Health Screening in the northern part of Singapore between September 2013 and December 2017. Of the 18,746 participants who were part of the health screening, 3,183 participants were included for analysis in this study (Figure 1). On average, the participants underwent 2-3 screenings with a follow-up period of 1.7 years. The study received ethics clearance from the National Healthcare Group Domain Specific Review Board in Singapore (Board (Ref. No. 2017/00735). Data was anonymized before analysis by the research team.

Information on demographics, smoking, exercise, stress coping strategies and medical history were obtained using a questionnaire administered to the participants as part of the screening. All readings were collected by community nurses and trained volunteers. Standing height and weight were obtained and body mass index (BMI) was calculated by dividing weight (in kg) by the square of height (in m^2). Sitting blood pressure after a resting period of at least 5 minutes was measured once with an automated sphygmomanometer (Omron, Japan) on the upper arm. Normal size soft cuffs (22-32 cm) were used except for individuals with obesity, for which the larger 32-42 cm soft cuffs were used. Morning fasting blood samples were collected from the participants, who had fasted for at least 9 hours overnight),and analysed at the hospital laboratory accredited by the Royal College of the American Pathologists. The following methods were used in the blood sample analysis: the hexominase method (Roche cobas® c701) for fasting plasma glucose (FPG), the enzymatic colorimeter test (Rocher cobas® c501) for high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG), and the Friedewald formula[19] for serum low-density lipoprotein cholesterol (LDL-C). The coefficients of variation (CV) for FPG were 0.5%-1.7% intra-assay and 0.4%-1.5% inter-assay. The CV for HDL-C were 0.4%-1.0% intra-assay and 0.9%-1.5% inter-assay, and the CV for TG were 0.7%-1.1% intra-assay and 1.6%-2.0% inter-assay.[20-22]



SBP, systolic blood pressure; DBP, diastolic blood pressure

Figure 1. Study population and exclusion criteria.

Exposure definition

The exposure variable, TyGI, was calculated using the formula by Simental-Mendia LE, et al.[12] : TyGI = Ln [fasting TG level (mg/dl)] x FPG (mg/dl)/2]. As there are no defined cut-offs for TyGI, participants were divided into quartiles according to their TyGI levels as follows: quartile (Q)1: 7.7-8.0); Q2: 8.1-8.3; Q3: 8.5-8.6; and Q4: 8.9-9.3.

Outcome definition

The outcome was the presence of hypertension defined as one of the following: systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, self-reported hypertension, or use of anti-hypertensive medications according to the World Health Organisation criteria.[23]

Statistical analysis

Categorical variables were expressed as frequencies (percentages). Continuous variables were expressed as mean (standard deviation) or median (interquartile range) depending on the distribution of variables. Additionally, TyGI was categorized into quartiles.

One-way analysis of variance and Student's t-test were used to compare the means of continuous variables across TyGI quartiles and hypertension status, respectively. Kruskal Wallis test and Mann-Whitney U test were used in lieu of these tests when the continuous variable had non-normal distribution. Chi-square test was used to compare the proportions of categorical variables across these groups.

Kaplan-Meier survival curves for incident hypertension stratified by TyGI quartiles were produced. These survival curves were compared using the log-rank test. On the other hand, Cox proportional-hazard regression was used to determine the association between TyGI and hypertension while controlling for age, gender, ethnicity and clinical covariates. Schoenfeld residuals were used to check if the proportional hazards assumption was violated.

Table 1. Baseline characteristics of participants stratified by triglyceride-glucose index (TyGI) in quartiles

Variable	All	TyGI quartile				
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p*
N	3183	805	793	790	795	
Age (years)	55.9 ± 8.1	54.7 ± 8.0	55.6 ± 8.0	56.6 ± 8.1	56.7 ± 8.3	<0.001
Male (%)	1035 (32.5)	155 (19.3)	209 (26.4)	288 (36.5)	383 (48.2)	<0.001
Ethnicity (%)						<0.001
Chinese	2776 (87.2)	715 (2.7)	724 (91.3)	682 (86.3)	655 (82.4)	
Malay	189 (5.9)	47 (5.8)	31 (3.9)	46 (5.8)	65 (8.2)	
Indian	144 (4.5)	21 (2.6)	24 (3.0)	45 (5.7)	54 (6.8)	
Other	74 (2.3)	22 (2.7)	14 (1.8)	17 (2.2)	21 (2.6)	
Exercise per week (%)						<0.001
120-150 mins	876 (27.5)	238 (29.6)	229 (28.9)	236 (29.9)	173 (21.8)	
60-90 mins	687 (21.6)	189 (23.5)	187 (23.6)	152 (19.2)	159 (20.0)	
30 mins	460 (14.5)	94 (11.7)	118 (14.9)	123 (15.6)	125 (15.7)	
<30 mins	1160 (36.4)	284 (35.3)	259 (32.7)	279 (35.3)	338 (42.5)	
Smoking (%)						<0.001
No	2970 (93.3)	772 (95.9)	753 (95.0)	730 (92.4)	715 (89.9)	
Yes	213 (6.7)	33 (4.1)	40 (5.0)	60 (7.6)	80 (10.1)	
Coping well with stress (%)						0.464
No	2174 (68.3)	551 (68.5)	558 (70.4)	528 (66.8)	537 (67.6)	
Yes	1009 (31.7)	254 (31.6)	235 (29.6)	262 (33.2)	258 (32.5)	
BMI (kg/m^2)	23.0 ± 3.6	21.4 ± 3.0	22.4 ± 3.4	23.6 ± 3.6	24.8 ± 3.4	<0.001
WC (cm)	81.6 ± 9.8	76.1 ± 8.4	79.7 ± 8.8	83.5 ± 9.3	87.3 ± 8.9	<0.001
SBP (mmHg)	120.1 ± 11.5	116.4 ± 11.9	119.6 ± 11.6	121.6 ± 10.8	123.0 ± 10.8	<0.001
DBP (mmHg)	72.1 ± 8.2	69.1 ± 7.9	71.5 ± 8.3	73.3 ± 7.8	74.5 ± 7.6	<0.001
LDL-C (mmol/l)	3.3 ± 0.9	2.9 ± 0.7	3.2 ± 0.8	3.5 ± 0.8	3.5 ± 0.9	<0.001
HDL-C (mmol/l)	1.6 ± 0.4	1.9 ± 0.4	1.7 ± 0.4	1.5 ± 0.4	1.3 ± 0.3	<0.001
TG (mmol/l)	1.0 (0.8-1.5)	0.6 (0.6-0.7)	0.9 (0.8-1.0)	1.2 (1.1-1.4)	1.9 (1.6-2.4)	<0.001
FPG (mmol/l)	5.3 ± 1.0	5.0 ± 0.4	5.2 ± 0.5	5.3 ± 0.6	5.9 ± 1.7	<0.001
TyGI	8.4 (8.1-8.8)	7.8 (7.7-8.0)	8.2 (8.1-8.3)	8.5 (8.5-8.6)	9.0 (8.9-9.3)	<0.001

TyGI, triglyceride-glucose index; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; FPG, fasting plasma glucose

Values presented as mean ± SD, frequencies (percentages), and median (IQR)

The role of TyGI on the association between BMI at baseline and the development of hypertension was assessed with mediation analysis. According to the Baron and Kenny framework,[24] mediation occurred if there were significant association between exposure and potential mediator, significant association between exposure and outcome and the association between exposure and outcome was attenuated when the potential mediator was included in the model. The two-sided tests performed were considered statistically significant if $p<0.05$. Analysis was done using STATA Version 14.0 (STATA Corp., College Station, TX, USA).

RESULTS

Table 1 shows the baseline characteristics of the study participants: age ($p<0.001$), BMI ($p<0.001$), SBP ($p<0.001$), DBP ($p<0.001$), LDL-C ($p<0.001$), TG ($p<0.001$) increased across TyGI quartiles, whereas HDL-C ($p<0.001$) decreased across TyGI quartiles. Study participants with higher TyGI quartiles tended to be males and non-Chinese ($p<0.001$). Those with higher TyGI quartiles were more likely to smoke and exercise less (≤30 mins per week) ($p<0.001$). Additionally of note, the overall mean HDL-C level was high and median TG level was low, potentially attributable to lower overall smoking rates (6.7%) and higher proportions who exercise at least 30 mins a week (63.6%).

After 5,380.07 person-years of follow-up, 363 study participants developed hypertension (11.4%) (Table 2). These study participants tended to be males and had poorer clinical profiles in terms of BMI, SBP, DBP, LDL-C, HDL-C, FPG and TyGI ($p<0.05$).

The survival curves for incident hypertension stratified by TyGI quartiles are shown in Figure 2. Results of the

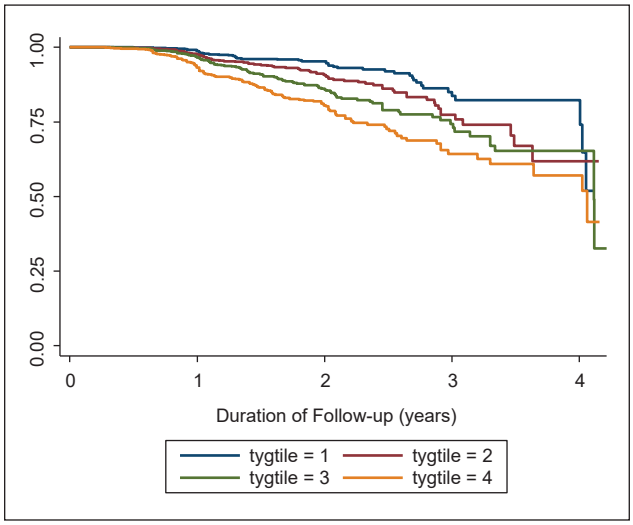


Figure 2. Kaplan-Meier survival curves by triglyceride-glucose quartiles.

log-rank test indicated that these survival curves were significantly different (p<0.001) with TyGI Q3 and Q4 having poorer disease-free survival compared to TyGI Q1 and Q2.

Table 2. Baseline characteristics of participants stratified according to the development of hypertension

Variable	Development of hypertension		
	No	Yes	*p*
N	2820	363	
Age (years)	55.4 ± 8.0	59.7 ± 8.3	<0.001
Male (%)	884 (31.4)	151 (41.6)	<0.001
Ethnicity (%)			0.816
Chinese	2462 (87.3)	314 (86.5)	
Malay	168 (6.0)	21 (5.8)	
Indian	127 (4.5)	17 (4.7)	
Other	63 (2.2)	11 (3.0)	
Exercise per week (%)			0.291
120-150 mins	775 (27.5)	101 (27.8)	
60-90 mins	613 (21.7)	74 (20.4)	
30 mins	396 (14.0)	64 (17.6)	
<30 mins	1036 (36.7)	124 (34.2)	
Smoking (%)			0.948
No	2631 (93.3)	339 (93.4)	
Yes	189 (6.7)	24 (6.6)	
Coping well with stress (%)			0.234
No	1936 (68.7)	238 (65.6)	
Yes	884 (31.4)	125 (34.4)	
BMI (kg/m^2)	22.9 ± 3.5	24.1 ± 3.9	<0.001
WC (cm)	81.2 ± 9.7	85.2 ± 10.1	<0.001
SBP (mmHg)	118.9 ± 11.3	129.9 ± 7.7	<0.001
DBP (mmHg)	71.3 ± 8.0	77.9 ± 7.1	<0.001
LDL-C (mmol/l)	3.3 ± 0.8	3.4 ± 0.9	0.002
HDL-C (mmol/l)	1.6 ± 0.4	1.5 ± 0.4	<0.001
TG (mmol/l)	1.0 (0.8-1.4)	1.2 (0.9-1.7)	<0.001
FPG (mmol/l)	5.3 ± 1.0	5.6 ± 1.3	<0.001
TyGI	8.3 (8.0-8.7)	8.6 (8.2-9.0)	<0.001

TyGI, triglyceride-glucose index; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; FPG, fasting plasma glucose

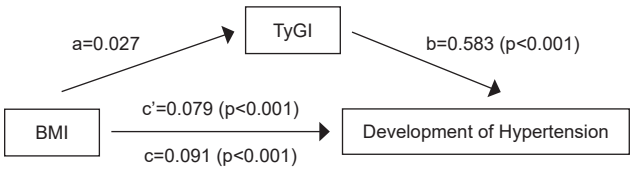
Values presented as mean ± SD, frequencies (percentages), and median (IQR)

The unadjusted Cox proportional hazard model (Table 3) showed that the hazard of hypertension increases with increasing TyGI. This hazard triples when the TyGI Q1 group is compared with the TyGI Q4 group (hazard ratio [HR]=3.31, 95% Confidence Interval [CI]: 2.38, 4.60). This association between higher TyGI quartiles and the development of hypertension remained statistically significant even after adjusting for demographics (Model 1) and baseline clinical covariates (Model 2), with the hazard for TyGI Q4 being more than double that of the TyGI Q1 (HR 2.57 (95%CI: 1.71, 3.87).

Mediation analysis (Figure 3) showed that BMI was associated with TyGI and the development of hypertension. Furthermore, there was attenuation of the relationship between BMI and development of hypertension with inclusion of TyGI in the model. After adjusting for age, gender, ethnicity and HDL-C, TyGI accounted for 16.4% of the relationship between BMI and development of hypertension (p<0.001).

DISCUSSION

Our findings revealed that higher TyGI was significantly associated with the development of hypertension. This was in line with the results from earlier research which showed that TyGI was a predictor of incident hypertension.[4,18]



Adjusted for age, gender, ethnicity and HDL-cholesterol.

Figure 3. Mediation of TyGI between baseline body mass index and the development of hypertension.

Table 3. Association between triglyceride-glucose (TyG) index in quartiles and the development of hypertension

Variable	Hazards Ratio (95% Confidence Interval)					
	Unadjusted	*p*	Model 1	*p*	Model 2	*p*
Age (per year)	1.06 (1.05, 1.08)	<0.001	1.06 (1.05, 1.07)	<0.001	1.06 (1.05, 1.08)	<0.001
Male	1.05 (1.22, 1.86)	<0.001	1.24 (1.00, 1.53)	0.046	1.34 (1.07, 1.68)	0.012
Ethnicity						
Chinese	0.92 (0.51, 1.68)	0.791	0.75 (0.41, 1.38)	0.355	0.85 (0.46, 1.56)	0.593
Malay	1.01 (0.49, 2.09)	0.982	0.85 (0.41, 1.77)	0.670	0.76 (0.36, 1.58)	0.460
Indian	1.03 (0.48, 2.19)	0.947	0.81 (0.38, 1.73)	0.585	0.81 (0.37, 1.74)	0.581
Other	1.00		1.00		1.00	
BMI (per kg/m^2)	1.08 (1.05, 1.11)	<0.001			1.08 (1.05, 1.11)	<0.001
LDL-C (per mmol/l)	1.20 (1.06, 1.35)	0.003			1.04 (0.91, 1.17)	0.577
HDL-C (per mmol/l)	0.67 (0.53, 0.86)	0.001			1.29 (0.93, 1.78)	0.126
TyGI						
Quartile 1	1.00		1.00		1.00	
Quartile 2	1.61 (1.12, 2.32)	0.010	1.56 (1.09, 2.25)	0.016	1.50 (1.03, 2.18)	0.035
Quartile 3	2.23 (1.58, 3.14)	<0.001	1.97 (1.40, 2.78)	<0.001	1.78 (1.22, 2.62)	0.003
Quartile 4	3.31 (2.38, 4.60)	<0.001	2.89 (2.07, 4.03)	<0.001	2.57 (1.71, 3.87)	<0.001

TyGI, triglyceride-glucose index; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol
Model 1 adjusted for age, gender, and ethnicity. Model 2 adjusted for age, gender, ethnicity, BMI, LDL-C, and HDL-C.

While the underlying mechanism for the relationship was not clear, there are a few possible explanations for insulin resistance conferring higher risk for the development of hypertension. First, insulin resistance enhances the activity of the sympathetic nervous system and increases the release of catecholamines, thereby causing thickening of the vascular smooth muscle and luminal stenosis.[25-28] The second possible explanation is that insulin resistance may lead to production and release of endothelin, narrowing blood vessels with less prostaglandin E2 and prostacyclin generated. This would then cause an increase in smooth muscle vasculature which would then elevate the blood pressure.[4,29,30] Third, insulin resistance enhances renin-angiotensin-aldosterone system activity and contributes to sodium reabsorption in the proximal tubule.[6,31-33] As TyGI was considered a surrogate of insulin resistance[9,10] and was also correlated positively with waist circumference (a marker of insulin resistance) in our study (correlational coefficient 0.457; $p<0.001$), it is then plausible that the above mechanisms accounted for the relationship between TyGI and the development of hypertension.

TyGI was observed to mediate the relationship between BMI and the development of hypertension in our study, suggesting partial contribution by TyGI, which is an indicator of insulin resistance, to the detrimental impact of BMI on the development of hypertension. Interestingly, an earlier study reported an interaction between TyGI and obesity on the risk of hypertension in middle-aged and elderly adults.[6] In our earlier study, TyGI was shown to mediate the association between BMI and the development of diabetes.[17] Thus it is plausible that TyGI partly accounted for the deleterious effects of BMI on cardiovascular and metabolic risk.

Our study has several strengths. First, this was a large community cohort. Second, mediation analysis was done to enhance our understanding of the role of the TyGI on the development of hypertension. However, because the large community cohort was used, we were limited by a relatively short follow-up period, retrospective design, and lack of data on insulin levels to confirm the mechanism underlying the association between insulin resistance and hypertension. Blood pressure was only measured once and a single reading could be misleading as BP is affected by transient external events. We also lacked information on alcohol intake which could potentially be a cofounding factor. Furthermore, while encouraged, repeat screenings were fully voluntary. This potentially led to some level of self-selection, with more motivated participants possibly following up more frequently.

TyGI is an inexpensive measure which is easily available in routine clinical practice. It may potentially be utilized to identify individuals at higher risk for hypertension, thereby enabling healthcare providers to form a stratified approach in the management through more targeted lifestyle interventions and medications. The mediating effect of TyG on the association between BMI and the development of hypertension also highlights the clinical importance of promoting a healthy body weight in an effort to reduce the risk of hypertension. Moving forward, it would be worth returning to this cohort after a longer time period to further explore the development of hypertension and other outcomes such as stroke, heart attack, and mortality. Our methodology is easily repeatable with other large health screening cohorts that can corroborate our observations.

CONCLUSION

In conclusion, triglyceride-glucose index was found to be an independent predictor of the development of hypertension and may potentially be used as an inexpensive indicator to predict the development of hypertension and risk-stratify individuals to aid management in clinical practice.

Statement of Authorship
The authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
JKCK: Conceptualization, Methodology, Formal Analysis, Investigation, Data Curation, Writing – original draft, Writing – review and editing, Visualization, Project Administration, Funding Acquisition; **SL:** Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Data Curation, Writing – original draft, Writing – review and editing, Visualization, Project Administration Funding Acquisition; **BI:** Conceptualization, Investigation, Resources, Writing – review and editing; **JIST:** Conceptualization, Validation, Writing – review and editing; **CFS:** Conceptualization, Writing – review and editing, Supervision; **TS:** Conceptualization, Writing – review and editing, Supervision; **SCL:** Conceptualization, Methodology, Writing – review and editing, Supervision

Author Disclosure
Prof. Su Chi Lim is supported by the Singapore Ministry of Health's National Medical Research Council under its Clinician Scientist Award (MOH-000714-01).

Drs. Khoo, Low, Irwan, Tang, Sum and Subramaniam declared no conflict of interest.

Funding Source
This work was supported by the Alexandra Health Enabling Grant (AHEG 2017/00735) provided by the Alexandra Health Fund.

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