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The triglyceride glucose index is associated with the cerebral small vessel disease in a memory clinic population

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ABSTRACT

Background and objectives: Insulin resistance (IR) has been associated with the cerebral small vessel disease (cSVD). However, as the surrogate marker of IR, there is little known about the relationship between the triglyceride glucose (TyG) index and cSVD. In this cross-sectional study, we aimed to evaluate the relationship between the TyG index and cSVD in a memory clinic population and explore the value of TyG index to improve the risk stratification of cSVD.

Methods: We included participants who attended our memory clinic from January 2016 to December 2020. TyG index was determined as ln [fasting triglyceride (mg/dL) × fasting plasma glucose (mg/dL)/2]. We assessed lacunes, microbleeds, white matter hyperintensity (WMH) and enlarged perivascular spaces (EPVS) on MRI and calculated the total cSVD burden.

Results: A total of 297 subjects were included (median age: 65 years, male sex: 64.98%). In the adjusted model, when dividing TyG index into quartiles, subjects with TyG index in the top quartile, compared with those in the bottom quartile, were more likely to have lacunes ($P = 0.035$), moderate-severe WMH ($P = 0.001$), a higher grade of deep WMH ($P = 0.004$), a higher grade of PVWMH ($P = 0.032$), a higher grade of EPVS ($P = 0.002$), and a higher cSVD score ($P < 0.001$). When introducing TyG index into traditional risk factors to predict moderate to severe cSVD, both area under the curve (0.745 vs 0.802, $P = 0.003$) and integrated discrimination index (0.080, 95% CI 0.050–0.110, $P < 0.001$) displayed an improvement from TyG index.

Conclusions: The TyG index is correlated with cSVD and may have the potential to be a surrogate marker of insulin resistance and optimize the risk stratification.

1. Introduction

Cerebral small vessel disease (cSVD) is a disorder of cerebral microvessels and its prevalence increases with age, affecting about 5% of people aged 50 years and almost everybody older than 90 years [1]. cSVD can be asymptomatic, however, its lesions can cause strokes, contribute to cognitive dysfunction, and lead to non-cognitive dysfunctions such as gait and balance loss, urinary incontinence, and mood disorders, seriously affecting the life quality of patients [2]. cSVD is often diagnosed based on neuroimaging markers, including recent small subcortical infarcts, lacunes, white matter hyperintensity (WMH), enlarged perivascular spaces (EPVS), cerebral microbleeds (CMBs), and cerebral atrophy [3]. Given the diverse distribution but the common coexistence of each neuroimaging marker, total cSVD scores are calculated by counting the presence of lacunes, WMH, EPVS, and CMBs to represent the total MRI burden and implicate the severity of cSVD. Understanding the etiology and pathogenesis of cSVD is essential for prevention and treatment, but they have not been fully elucidated. Although studies revealed that the traditional vascular risk factors, such as age, male sex, smoking, hypertension, and diabetes mellitus (DM), were related to the cSVD burden [4–6], they are far from sufficient and accurate to capture the risks of cSVD.

Insulin resistance (IR) is a pathological condition with reduced sensitivity in body tissues to the action of insulin [7]. It is not only the core defect in type 2 DM but also plays a role in metabolic syndrome [8], atherosclerotic cardiovascular disease [9], ischemic stroke [9,10] and neurodegenerative diseases like Alzheimer's disease [11]. Recent studies revealed that IR estimated by the homeostasis model assessment

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of insulin resistance (HOMA-IR) was associated with the imaging markers of cSVD, including EPVS [12], lacunes [13,14] and WMH [15]. Further, IR was found to be associated with the total cSVD burden [16] and vascular cognitive impairment in cSVD patients [17]. However, whether IR is useful in risk stratification for cSVD in clinical practice remains unknown. Additionally, the use of HOMA-IR is limited by the inconvenience of insulin quantitative measurement. As an alternative, the triglyceride glucose (TyG) index has recently been proposed. It is calculated conveniently by fasting total triglyceride (TG) and fasting plasma glucose (FPG) and shows a good correlation with HOMA-IR[18]. A recent study demonstrated that the TyG index was associated with silent brain infarcts and WMH in a healthy population [15], but the correlation of the TyG index with other neuroimaging markers and the global burden of cSVD is little known.

Therefore, in this study, we investigated the potential relationship between TyG index and cSVD and further evaluated the value of TyG index to optimize the risk stratification of the moderate to severe cSVD based on a memory clinic population.

2. Methods

2.1. Subjects

We retrospectively collected data from patients attending the memory clinic in Hebei General Hospital from January 2016 to December 2020. We included all patients who had the blood biochemistry indexes and underwent complete magnetic resonance imaging (MRI) sequences necessary for evaluating cSVD markers at the same visit. The exclusion criteria are as follows: used glucose-lowering or lipid-lowering agents, history of severe ischemic or hemorrhagic stroke or other neurologic disorders (such as neurotrauma and brain tumor) affecting the MRI assessment for cSVD, acute stroke/transient ischemic attack (TIA) or other neurologic disorders (such as epilepsy and infection) causing transient hyperglycemia in the stress condition, significant infection, malignant diseases, thyroid and adrenal cortex dysfunction, hematologic disorders, autoimmune diseases, severe hepatic or nephritic dysfunction, and surgery or trauma 3 months before admission. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethical Committees of Hebei General Hospital.

2.2. Clinical assessments and risk factor definitions

At baseline, we collected the following variables: demographic profiles (age, gender, height, and weight), medical history (hypertension, stroke/TIA, coronary heart disease, dyslipidemia, and DM), history of smoking, and alcohol consumption. All these characteristics were obtained through face-to-face inquiry by the neurological doctor. Body mass index (BMI) was calculated as body weight divided by squared height. Hypertension was defined as self-reported hypertension diagnosis, use of anti-hypertensive medications, or recorded systolic blood pressure $\geq$ 140 mmHg and/or diastolic blood pressure $\geq$ 90 mmHg for two or more successive times [19]. Dyslipidemia was diagnosed for total cholesterol $\geq$ 6.2 mmol/L, low-density lipoprotein cholesterol (LDL-C) $\geq$ 4.1 mmol/L, self-reported dyslipidemia diagnosis, or a history of use of lipid-lowering agents [20]. DM was defined as FPG $\geq$ 7.0 mmol/L, random plasma glucose $\geq$ 11.1 mmol/L, hemoglobin A1c (HbA1c) $\geq$ 7.0%, self-reported DM diagnosis, or use of glucose-lowering agents [21]. Current or former smoking was diagnosed if a man has smoked 100 cigarettes in his or her lifetime with or without quitting smoking at present. Alcohol consumption was defined as consuming alcohol 12 or more times within the past year. Venous blood samples were taken from subjects who fasted for at least 8 h for laboratory examination. FPG, TG, total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), HbA1c, homocysteine, creatinine, and uric acid were recorded. The TyG index was calculated as ln [TG (mg/dL) $\times$ FPG (mg/dL)/2] [18].

2.3. Neuroimaging assessments

MRI performed in all subjects used 3.0 T MR scanners (Signa, GE Healthcare of American). The MRI protocol included T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), fluid-attenuated inversion recovery (FLAIR), and susceptibility-weighted imaging (SWI). MR scanning parameters: T1WI: repetition time (TR)/echo time (TE) = 1909/20.2 ms (ms), slice thickness = 5 mm; T2WI: TR/TE = 5000/125 ms, slice thickness = 5 mm; FLAIR: TR/TE = 8,502/159.4 ms, slice thickness = 5 mm; SWI: TR/TE = 78.6/47.6 ms, slice thickness = 2 mm.

Two experienced neurologists independently evaluated images according to the Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) criteria [22] and were blinded to the clinical data. The interrater κ values were 0.81 for deep CMB, 0.87 for lobar CMB and 0.90 for lacunes. The interrater weighted κ values were 0.72 for EPVSs, 0.88 for PVWMH and 0.82 for deep WMH. Discrepancies were resolved by a third neurologist. Lacune was counted and diagnosed as a round or ovoid, subcortical cavity, with a signal similar to cerebrospinal fluid and a diameter of between 3 mm and 15 mm, following the territory of a perforating arteriole. EPVS was similar to the lacune but measured <3 mm, and without a hyperintense rim on FLAIR. EPVSs were counted in the basal ganglia and stratified as follows: 1 = 0–10 EPVSs, 2 = 11–25 EPVSs, and 3 = >25 EPVSs [12]. WMH was defined as bilateral, mostly symmetric hyperintensities on T2WI. The periventricular WMH (PVWMH, range 0–3) and the deep WMH (range 0–3) were rated on the Fazekas rating scale using FLAIR and T2WI sequences [23]. Moderate-severe WMH was defined when PVWMH scored = 3 or deep WMH scored = 2/3. CMB was diagnosed as a small area of signal void on SWI with a diameter no >10 mm. In our study, we separately assessed lobar CMBs and deep CMBs because they are supposed to differ in pathophysiology [24].

We evaluated the total cSVD burden based on a 4-point cSVD burden scale. One point was given for the presence of each of the following markers: one or more lacunes located in the internal or external capsule, basal ganglia, thalamus, or brain stem; one or more deep CMBs located in the internal or external capsule, basal ganglia or thalamus; PVWMH with a Fazekas score of 3 or deep WMH with a Fazekas score of 2 or 3; EPVS with a scale of 2 or 3. According to their total cSVD scores, patients were further assigned into absent/mild (with a score of 0 or 1), moderate (with a score of 2), or severe (with a score of 3 or 4) total cSVD burden group.

2.4. Statistical analysis

Continuous variables with normal distributions were presented as mean $\pm$ standard deviation and those with non-normal distributions were presented as median (interquartile range [IQR]). Categorical variables were presented as frequency (percentage). To compare characteristics by quartile of TyG index, we used the chi-square test (χ^2) or Spearman correlation analysis for comparisons of categorical variables and one-way analysis of variance (ANOVA) or Kruskal-Wallis test for comparisons of continuous variables. We assessed the association between the TyG index and lacunes, deep and lobar CMBs, and moderate-severe WMH using univariate and multivariable binary logistic regression analysis. Univariate and multivariable ordinal logistic regressions were used to assess the correlation between TyG index and PVWMH, deep WMH, EPVS and the total cSVD burden. The odds ratio (OR) and 95% confidence interval (CI) were obtained. In multivariable analysis, we adjusted for variables with P values < 0.10 in the univariable analysis. The value of TyG to improve the risk stratification of the moderate to severe cSVD was first evaluated by receiver operating characteristic curve (ROC) analysis. Then to better quantify the improvement in the risk stratification offered by the models with TyG index, integrated discrimination improvement (IDI) was calculated [25]. The traditional risk factors were introduced to the model of risk stratification if P values < 0.10 in the univariable analysis or be considered clinically relevant.

All statistical analyses above were performed with IBM SPSS Statistics for Windows software (Version 22.0, IBM Corp., Armonk, NY, USA) and MedCalc for Windows software (version 19.4, Ostend, Belgium). The results were recognized statistically significant when $P < 0.05$.

3. Results

3.1. Characteristics of subjects

We finally collected 297 subjects in our study. The median age of the subjects was 65 years (IQR, 59.0–70.0 years), and 64.98% of the subjects were male. Vascular risk factors such as hypertension, current or former smoking, and alcohol consumption were frequent among all of the patients (72.05, 31.31, and 27.61%, respectively), whereas fewer patients had other vascular risk factors, including untreated DM, previous stroke/TIA, coronary heart disease, and untreated dyslipidemia (12.46, 11.11, 11.11 and 6.73%, respectively). The proportions of the patients with total cSVD scores of 0, 1, 2, 3, and 4 were 15.49, 25.58, 27.61, 19.87, and 11.45%, respectively. And the composition of categories for each cSVD score was shown in Fig. 1.

Table 1 showed the demographic and clinical characteristics of all the included subjects divided by quartile of TyG index. Among all the subjects, TyG index was associated with BMI ($P < 0.001$), DM ($P > 0.001$), TC ($P = 0.001$), TG ($P < 0.001$), HDL-C ($P = 0.014$), LDL-C ($P < 0.001$), HbA1c ($P < 0.001$), FPG ($P < 0.001$), uric acid ($P = 0.011$), and creatinine ($P = 0.040$). With regard to the neuroimaging, the distributions of moderate-severe WMH, EPVS grade, and total cSVD burden had significant differences ($P = 0.018$, $P = 0.001$, and $P = 0.001$, respectively), and the distribution of lacunes and deep WMH showed a tendency toward statistical significance ($P = 0.079$ and $P = 0.055$, respectively). However, there were no differences in PVWMH, lobar CMBs or deep CMBs by TyG index quartiles.

3.2. Association between TyG index and cSVD imaging markers

We used logistic regression analysis to assess the association of TyG index with neuroimaging markers of cSVD (Table 2). We first conducted regression analysis using the standard deviation transformed TyG index as a continuous variable. For a per-SD increase in TyG index, the ORs in univariate regression analysis were 1.352 (95% CI 1.056–1.730, $P = 0.017$) for deep CMBs, 1.404 (95% CI 1.108–1.779, $P = 0.005$) for moderate-severe WMH, 1.311 (95% CI 1.066–1.613, $P = 0.010$) for a higher grade of deep WMH, and 1.456 (95% CI 1.170–1.811, $P = 0.001$) for a higher grade of EPVS. In multivariable regression analysis, the association between TyG index and deep CMBs, moderate-severe WMH, deep WMH and EPVS remained significant. There was also a relationship between TyG index and PVWMH (OR 1.361, 95% CI 1.093–1.696, $P = 0.006$) in multivariable regression analysis. Then we explored the relationship between the TyG index and neuroimaging markers of cSVD by categorizing the TyG index into quartiles and using the first quartile as the reference. TyG index was positively associated with moderate-severe WMH ($P_{trend} = 0.008$, $P_{trend} = 0.002$, respectively), deep WMH ($P_{trend} = 0.029$, $P_{trend} = 0.008$, respectively), and EPVS ($P_{trend} = 0.006$, $P_{trend} = 0.001$, respectively) in univariate and multivariable regression analysis, with a significant trend across the quartiles. In univariate regression analysis, there was also a significant trend across the quartiles for lacunes ($P = 0.019$), but in multivariable regression analysis, there was no significance ($P = 0.069$). Compared with subjects with a TyG index of Q1, the subjects with a TyG index of Q4 were more likely to have lacunes (crude: OR 2.522, 95% CI 1.213–5.244, $P = 0.013$; adjusted: OR 2.409, 95% CI 1.064–5.455, $P = 0.035$), moderate-severe WMH (crude: OR 2.705, 95% CI 1.390–5.263, $P = 0.003$; adjusted: OR 3.634, 95% CI 1.662–7.946, $P = 0.001$), a higher grade of deep WMH (crude: OR 2.115, 95% CI 1.182–3.785, $P = 0.012$; adjusted: OR 2.537, 95% CI 1.356–4.745, $P = 0.004$), a higher grade of PVWMH (adjusted: OR 1.948, 95% CI 1.058–3.593, $P = 0.032$) and a higher grade of EPVSs (crude: OR 2.188, 95% CI 1.192–4.011, $P = 0.011$; adjusted: OR 2.606, 95% CI 1.401–4.850, $P = 0.002$).

3.3. Association between TyG index and total cSVD burden

We also employed ordinal logistic regression to demonstrate the association between TyG index and the total cSVD burden (Table 3). In the crude model, for a per-SD increase in TyG index, the OR was 1.602 (95% CI 1.300–1.974, $P < 0.001$) for a higher cSVD score. After full adjustment, the risk attenuated into 1.737 (95% CI 1.365–2.212, $P < 0.001$). When dividing TyG index into quartiles, the subjects with the top quartile were more likely to have a higher cSVD score against the bottom quartile (crude: OR 3.518, 95% CI 1.958–6.315, $P < 0.001$; adjusted: OR 4.216, 95% CI 2.181–8.150, $P < 0.001$), and we also observed significant trends across the quartiles (both $P_{trend} < 0.001$).

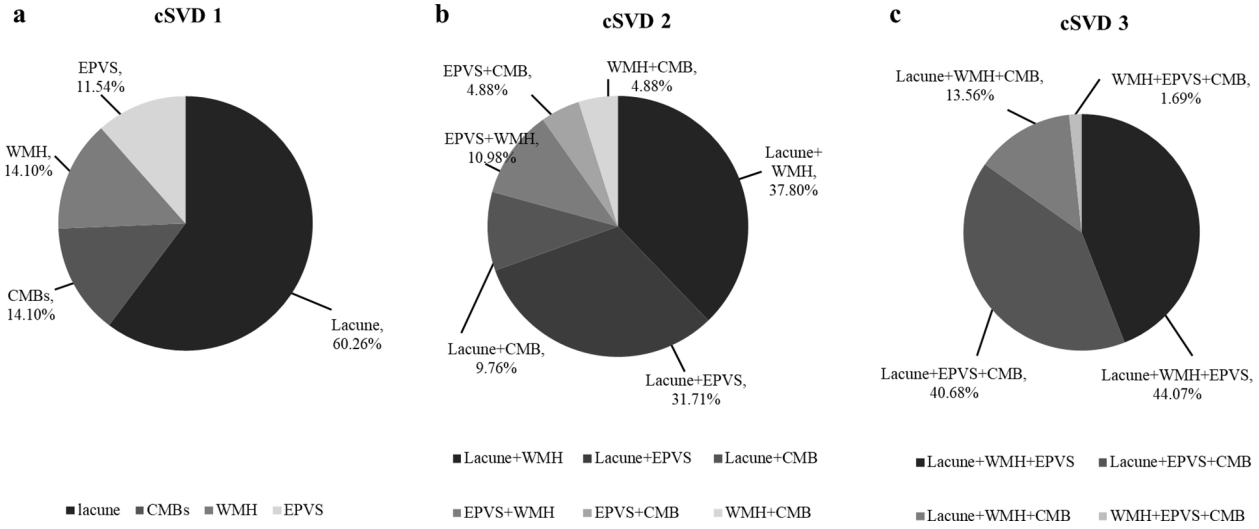

Fig. 1. The frequencies of cSVD markers according to different categories of cSVD score. (A) 1 marker of cSVD, (B) 2 markers of cSVD, (C) 3 markers of cSVD, 0 and 4 markers were not shown for none or all markers existed. Abbreviations: CMB, cerebral microbleed; WMH, white matter hyperintensity; EPVS, enlarged perivascular space; cSVD, cerebral small vessel disease.

Table 1
Demographic and clinical characteristics of subjects divided by quartile of TyG index.

Variables	ALL (n = 297)	TyG index quartiles				*P*-value[a]
		Q1(n = 75)	Q2(n = 73)	Q3(n = 74)	Q4(n = 75)	
Demographic data						
Age, years	65.00(59.00,70.00)	66.00(62.00,71.00)	65(60.50,70.00)	64.00(55.00,68.25)	64.00(56.00,70.00)	0.369
Male, *n* (%)	193(64.98)	51(68.00)	46(63.01)	49(66.22)	47(62.67)	0.885
Risk factors						
Body mass index, kg/m^2	25.48 ± 3.27	24.31 ± 3.10	25.27 ± 3.31	25.23 ± 2.70	27.10 ± 3.34	< 0.001
Alcohol consumption, *n* (%)	82(27.61)	21(28.00)	19(26.68)	19(25.68)	23(30.67)	0.900
Current or former smoking, *n* (%)	93(31.31)	25(33.33)	22(30.14)	25(33.78)	21(28.00)	0.854
Hypertension, *n* (%)	214(72.05)	55(73.33)	48(65.75)	55(74.32)	56(74.67)	0.584
History of stroke/TIA, *n* (%)	33(11.11)	6(8.00)	11(15.07)	8(10.81)	8(10.67)	0.590
History of coronary heart disease, *n* (%)	33(11.11)	10(13.33)	5(6.85)	11(14.86)	7(9.33)	0.390
Untreated dyslipidemia, *n* (%)	20(6.73)	4(5.33)	3(4.11)	5(6.76)	8(10.67)	0.475
Untreated diabetes mellitus, *n* (%)	37(12.46)	5(6.67)	7(9.59)	3(4.05)	22(29.33)	< 0.001
Laboratory examination						
Total cholesterol, mmol/L	4.54 ± 0.99	4.17 ± 0.91	4.54 ± 0.90	4.64 ± 0.88	4.80 ± 1.15	0.001
Total triglyceride, mmol/L	1.21(0.90,1.65)	0.76(0.63,0.86)	1.00(0.94,1.16)	1.44(1.33,1.64)	2.10(1.61,2.64)	< 0.001
HDL-C, mmol/L	1.10(0.95,1.26)	1.13(1.00,1.39)	1.14(0.98,1.32)	1.07(0.96,1.20)	1.03(0.91,1.20)	0.014
LDL-C, mmol/L	2.94 ± 0.74	2.64 ± 0.69	2.95 ± 0.68	3.05 ± 0.66	3.13 ± 0.85	< 0.001
Hemoglobin A1c, %	5.96(5.70,6.21)	5.87(5.60, 6.21)	5.87(5.60,6.21)	5.96(5.70,6.20)	6.20(5.90,6.70)	< 0.001
Fasting glucose, mmol/L	4.99(4.51,5.76)	4.56(4.31,4.96)	4.97(4.47, 5.43)	5.05(4.62,5.47)	5.98(4.95,7.00)	< 0.001
Homocysteine, mmol/L	14.50(11.15,20.55)	15.00(11.70,21.50)	14.80(10.10,19.25)	14.85(11.18,22.53)	13.80(11.30,22.90)	0.683
Uric acid, mmol/L	312.90 ± 82.09	297.63 ± 74.34	299.38 ± 68.17	313.19 ± 80.34	341.07 ± 96.54	0.011
Creatinine, mmol/L	70.97 ± 14.38	73.64 ± 16.03	68.64 ± 15.03	73.06 ± 12.00	68.51 ± 13.61	0.040
Imaging data						
Lacune	203(68.35)	46(61.33)	48(65.75)	49(66.22)	60(80.00)	0.079
Deep CMBs	94(31.65)	20(26.67)	21(28.77)	22(29.73)	31(41.33)	0.211
Lobar CMBs	73(24.58)	15(20.00)	19(26.03)	16(21.62)	23(30.67)	0.118
Periventricular WMH						0.423
0	65(21.89)	18(24.00)	16(21.92)	17(22.97)	14(18.67)	
1	107(36.03)	28(37.33)	26(35.62)	29(39.19)	24(32.00)	
2	62(20.88)	14(18.67)	14(19.18)	17(22.97)	17(22.67)	
3	63(21.21)	15(20.00)	17(23.29)	11(14.86)	20(26.67)	
Deep WMH						0.055
0	64(21.55)	19(25.33)	15(20.55)	16(21.62)	14(18.67)	
1	97(32.66)	34(45.33)	20(27.40)	22(29.73)	21(28.00)	
2	82(27.61)	12(16.00)	22(30.14)	26(35.14)	22(29.33)	
3	54(18.18)	10(13.33)	16(21.92)	10(13.51)	18(24.00)	
Moderate-severe WMH[b]	140(47.14)	24(32.00)	38(52.05)	36(48.65)	42(56.00)	0.018
EPVS grade						0.001
1	181(60.94)	53(70.67)	54(73.97)	41(55.41)	33(44.00)	
2	92(30.64)	14(18.67)	15(20.55)	28(37.84)	34(45.33)	
3	25(8.42)	8(10.67)	4(5.48)	5(6.76)	8(10.67)	
Total cSVD burden						0.001
0	46(15.49)	14(18.67)	11(15.07)	13(17.57)	8(10.67)	
1	76(25.58)	30(40.00)	20(27.40)	14(18.92)	12(16.00)	
2	82(27.61)	14(18.67)	24(32.88)	22(29.73)	22(29.33)	
3	59(19.87)	14(18.67)	14(19.18)	18(24.32)	13(17.33)	
4	34(11.45)	3(4.00)	4(5.48)	7(9.46)	20(26.67)	

Data are expressed as mean ± standard deviation or median (interquartile range) and numbers (percentage) as appropriate.
[a] Comparisons of categorical variables between groups were tested by chi-square test or Spearman correlation analysis and comparisons of continuous variables between groups were tested by one-way analysis of variance or Kruskal-Wallis test.
[b] With PVWMH scored 3 or deep WMH scored 2 or 3.

3.4. Value of TyG index to improve the risk stratification of cSVD

To evaluate the value of TyG to optimize the risk stratification of moderate to severe cSVD, we performed ROC analysis and calculated IDI (Fig. 2, Table 4). The area under the curve (AUC) of TyG index for moderate to severe cSVD was 0.636 (95% CI 0.572–0.700, $P < 0.001$). Compared with traditional risk factors (including age, sex, hypertension, history of stroke/TIA, current or former smoking, untreated dyslipidemia, untreated DM, homocysteine, and uric acid) only, we found a significant improvement of AUC after adding TyG index [0.745 (0.692,0.794) vs 0.802(0.752,0.846), $P = 0.003$]. In reclassification analysis, we also found significant advancement in IDI (0.080 95% CI 0.050–0.110, $P < 0.001$) when adding TyG index into the above traditional risk.

4. Discussion

In this retrospective cross-sectional study, we revealed that TyG index was associated with cSVD imaging markers and the total cSVD burden in the memory clinic population. Additionally, our results also showed that when introducing TyG index into established traditional risk factors, the risk identifying ability of the moderate to severe cSVD was significantly improved.

There has been increasing evidence demonstrating that IR is associated with cSVD [12,13,14,15,16]. In addition to DM, patients with IR are prone to obesity, hypertension, dyslipidemia, hyperuricemia,

Table 2
Correlation between TyG index and neuroimaging markers of cSVD in univariate and multivariable binary/ordinal logistic regression analysis.

		Odds Ratios (95% confidence intervals)			
		Crude	*P* value	Adjusted	*P* value
Lacune[a]	TyG (Per SD increase)	1.283 (0.995,1.654)	0.055	1.212 (0.905,1.625)	0.197
	Quartiles of TyG				
	Quartile 1	1.00	–	1.00	–
	Quartile 2	1.210 (0.619,2.367)	0.577	1.456 (0.705,3.006)	0.310
	Quartile 3	1.236 (0.633,2.413)	0.536	1.233 (0.602,2.526)	0.567
	Quartile 4	2.522 (1.213,5.244)	0.013	2.409 (1.064,5.455)	0.035
	P for trend	–	0.019		0.069
Deep CMB[b]	TyG (Per SD increase)	1.352 (1.056,1.730)	0.017	1.326 (1.027,1.711)	0.030
	Quartiles of TyG				
	Quartile 1	1.00	–	1.00	–
	Quartile 2	1.111 (0.540,2.282)	0.775	1.180 (0.566,2.459)	0.658
	Quartile 3	1.163 (0.569,2.377)	0.678	1.148 (0.553,2.381)	0.712
	Quartile 4	1.937 (0.974,3.855)	0.059	1.819 (0.891,3,711)	0.100
	P for trend	–	0.062	–	0.120
Lobar CMB[c]	TyG (Per SD increase)	1.247 (0.959,1.621)	0.099	1.187 (0.887,1.587)	0.249
	Quartiles of TyG				
	Quartile 1	1.00	–	1.00	–
	Quartile 2	1.407 (0.651,3.041)	0.385	1.464 (0.671,3.197)	0.338
	Quartile 3	1.103 (0.500,2.435)	0.807	1.076 (0.484,2.393)	0.857
	Quartile 4	1.769 (0.837,3.742)	0.135	1.613 (0.726,3.584)	0.240
	P for trend		0.214		0.393
Moderate-severe WMH[d]	TyG (Per SD increase)	1.404 (1.108,1.779)	0.005	1.625 (1.224,2.156)	0.001
	Quartiles of TyG				
	Quartile 1	1.00	–	1.00	–
	Quartile 2	2.307 (1.183,4.500)	0.014	2.533 (1.168,5.494)	0.019
	Quartile 3	2.013 (1.035,3.917)	0.039	2.481 (1.154,5.336)	0.020
	Quartile 4	2.705 (1.390,5.263)	0.003	3.634 (1.662,7.946)	0.001
	P for trend	–	0.008	–	0.002
PVWMH[e]	TyG (Per SD increase)	1.185 (0.964,1.456)	0.107	1.361 (1.093,1.696)	0.006
	Quartiles of TyG				
	Quartile 1	1.00	–	1.00	–
	Quartile 2	1.169 (0.654,2.092)	0.598	1.294 (0.698,2.400)	0.413
	Quartile 3	0.944 (0.528,1.685)	0.844	1.125 (0.615,2.057)	0.702
	Quartile 4	1.484 (0.833,2.646)	0.181	1.948 (1.058,3.593)	0.032
	P for trend	–	0.303		0.060
Deep WMH[f]	TyG (Per SD increase)	1.311 (1.066,1.613)	0.010	1.423 (1.141,1.777)	0.002
	Quartiles of TyG				
	Quartile 1	1.00	–	1.00	–
	Quartile 2	1.929 (1.074,3.463)	0.028	2.035 (1.103,3.755)	0.023
	Quartile 3	1.553 (0.868,2.776)	0.138	1.793 (0.985,3.264)	0.056
	Quartile 4	2.115 (1.182,3.785)	0.012	2.537 (1.356,4.745)	0.004
	P for trend	–	0.029		0.008
EPVS[g]	TyG (Per SD increase)	1.456 (1.170,1.811)	0.001	1.585 (1.266,1.985)	< 0.001
	Quartiles of TyG				
	Quartile 1	1.00	–	1.00	–
	Quartile 2	0.827 (0.447,1.528)	0.543	0.882 (0.472,1.647)	0.692
	Quartile 3	1.192 (0.649,2.190)	0.572	1.323 (0.713,2.457)	0.375
	Quartile 4	2.188 (1.192,4.011)	0.011	2.606 (1.401,4.850)	0.002
	P for trend	–	0.006	–	0.001

Abbreviations: TyG, triglyceride glucose index; cSVD, cerebral small vessel disease; CMB, cerebral microbleed; WMH, white matter hyperintensity; PVWMH, periventricular white matter hyperintensity; EPVS, enlarged perivascular space; SD, standard deviation.
Crude: no adjustment;
[a] Adjusted with $P < 0.10$ in the univariable analysis (age, sex, hypertension, current or former smoking, alcohol consumption, hemoglobin A1c, creatinine, homocysteine).
[b] Adjusted with $P < 0.10$ in the univariable analysis (age, hypertension, uric acid).
[c] Adjusted with $P < 0.10$ in the univariable analysis (history of coronary heart disease, homocysteine, hemoglobin A1c).
[d] With PVWMH scored 3 or deep WMH scored 2 or 3. Adjusted with $P < 0.10$ in the univariable analysis (age, hypertension, alcohol consumption, history of stroke/transient ischemic attack, history of coronary heart disease, creatinine, homocysteine).
[e] Adjusted with $P < 0.10$ in the univariable analysis (age, sex, hypertension, history of stroke/transient ischemic attack, creatinine, homocysteine).
[f] Adjusted with $P < 0.10$ in the univariable analysis (age, hypertension, history of stroke/transient ischemic attack, homocysteine, history of coronary heart disease, creatinine, uric acid).
[g] Adjusted with $P < 0.10$ in the univariable analysis (age, hypertension, history of coronary heart disease).

Table 3
Correlation between TyG index and the total cSVD burden in univariate and multivariable ordinal logistic regression.

Variables	Odds Ratios (95% confidence intervals)			
	Crude	*P* value	Adjusted*	*P* value
TyG (Per SD increase)	1.602 (1.300,1.974)	< 0.001	1.737 (1.365,2.212)	< 0.001
Quartiles of TyG				
Quartile 1	1.00		1.00	
Quartile 2	1.451 (0.815,2.583)	0.206	1.768 (0.971,3.222)	0.062
Quartile 3	1.850 (1.040,3.294)	0.037	2.094 (1.158,3.785)	0.014
Quartile 4	3.518 (1.958,6.315)	< 0.001	4.216 (2.181,8.150)	< 0.001
P for trend		< 0.001		< 0.001

Abbreviations: TyG, triglyceride glucose index; cSVD, cerebral small vessel disease; SD, standard deviation.
* Adjusted with $P < 0.10$ in the univariable analysis (age, sex, hypertension, history of stroke/transient ischemic attack, hemoglobin A1c, creatinine, homocysteine, uric acid).

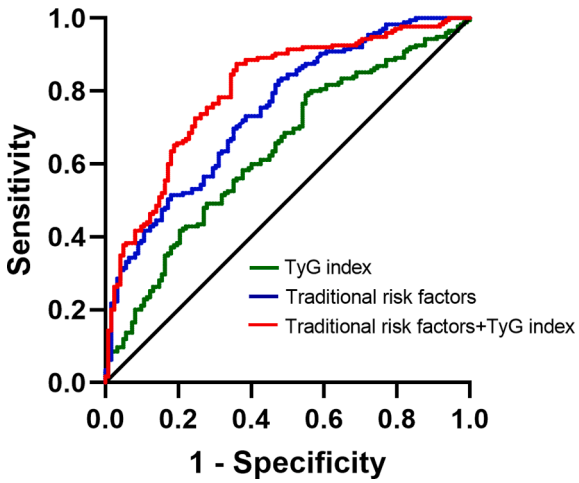

Fig. 2. Receiver operating characteristic curves for TyG to improve the risk stratification of moderate to severe cSVD. The optimal TyG cutoff values for the presence of moderate to severe cSVD were detected by maximizing Youden's index. The optimal TyG cutoff value for detection of the presence of moderate to severe cSVD was 8.24 with a sensitivity of 78.86% and a specificity of 45.08% (AUC = 0.636, 95% CI 0.572–0.700, $P < 0.001$). The AUC for the model with traditional risk factors are 0.745 (95% CI 0.692–0.794, $P < 0.001$). When adding the TyG index into the model, the AUC increased to 0.802 (95% CI 0.752–0.846, $P < 0.001$) and the improvement is significant ($P = 0.003$). Abbreviations: TyG: triglyceride-glucose index; cSVD, cerebral small vessel disease; AUC: area under the curve; 95% CI: 95% confidence interval.

atherosclerosis, and so on [26]. All these above are risk factors related to cerebrovascular disease, including cSVD. Therefore, early identifying the patients with IR may help to delay the cSVD progression. At present, the gold standard to assess IR is hyperinsulinemia euglycemic clamp (HIEC), which is invasive, time-consuming, expensive, and requires experienced operators [27]. HOMA-IR is another widely used surrogate marker for IR. However, it requires quantification of insulin, which is relatively difficult and often unavailable. It is increasingly evident that TyG index may have a better cost/performance ratio in assessing IR. For the performance, TyG index showed a significant association with HIEC and HOMA-IR to identify IR in different ethnic groups [28–30]. In some cases, TyG index acted even better than HOMA-IR did [31–34]. For expense, the cost of measuring HOMA-IR index is about 13 euros, while the cost of measuring TyG index is <5 euros, allowing a clear decrease in expense [35] Nevertheless, the relationship between the TyG index and cSVD has not been systemically evaluated, and even less information exists regarding the value of TyG index to optimize the risk stratification of cSVD.

Compared to previous studies, an important advantage of our study was to assess the relationship between TyG index and each cSVD imaging marker. Consistently with the previous study in a healthy population [15], we found TyG index was associated with WMH. We also revealed that TyG index was closely related to lacunes, deep CMBs and EPVS, which is consistent with the study measuring IR by HOMA-IR [12–15]. Previous studies reported that both CMBs and WMH in different locations might have different pathophysiology [24,36]. Therefore, we differentiated CMB and WMH lesions based on their locations to further evaluate their relationships with TyG index. In our study, the standard deviation transformed TyG index was significantly associated with the deep CMBs rather than lobar CMBs. Deep CMB is reported to be more associated with hypertensive vascular disease. Interestingly, the correlation between TyG index and hypertension has been widely confirmed in the past [37], which supported our finding. Frustratingly, we did not observe the relationship between TyG index and hypertension in our study. The unexpected outcomes may be attributable to the characteristics of the participants we chose. Our study excluded the subjects with a history of glucose-lowering or lipid-lowering agent use, who may have a higher frequency of hypertension. Lobar CMB is more associated with cerebral amyloid angiopathy. Though IR could contribute to the formation of amyloid β (Aβ) [11], our findings may not support the hypothesis that IR is associated with cSVD via amyloid angiopathy. As for WMH lesions, TyG index was not only associated with PVWMH but also with deep WMH. PVWMH are related to alterations in long perforating arteries and associated with hypoperfusion and risk factors of the large vessel disease, such as smoking, drinking, and hypercholesterolemia. Deep WMH occur in the subcortex, areas primarily supplied by the short branch arteries coming from the long perforating arteries, thus are more related to the risk factors attributing to the small vessel disease, such as hypertension [38]. Our study on WMH reconfirmed the noticeable role of TyG index in small vessel disease.

To our knowledge, this is the first study exploring the association between TyG index and total cSVD burden. Compared with the individual cSVD markers, the total cSVD burden combining all the cSVD markers can better capture the overall effects of cSVD on the brain, thus being more representative. To index the total cSVD burden, we used a widely-used 4-point cSVD burden scale in our study, whose construct validity has been confirmed [4,39,40]. We found TyG index was significantly associated with total cSVD burden after controlling for several confounders, reconfirming that IR is a risk factor of cSVD. Although the mechanism remains elusive, several possible mechanisms may explain this effect. One explanation may involve the blood–brain barrier (BBB) dysfunction. A hallmark of IR is endothelial dysfunction with a reduced nitric oxide (NO) bioavailability and increased endothelin-1 (ET-1) secretion [41], which would lead to a functional suppression of the BBB. IR can also promote oxidative stress, endoplasmic reticulum stress, mitochondrial dysfunction, leukocyte recruitments and pro-inflammatory cytokine activation [42–44], resulting in the BBB breakdown. Recently, there is also evidence that IR can destroy the BBB through chronic activation of endothelial adenosine receptor 2a[45] and downregulation of expression levels of tight-junction proteins (claudin-5, occludin) [46]. BBB dysfunction caused by IR, irrespective of the manners, may lead to the leakage of toxic materials into the perivascular tissues and hinder the waste removed by the glymphatic system[2], resulting in the development of cSVD. Reduced cerebral blood flow (CBF) may be another underlying mechanism. IR can diminish NO production and increase ET-1 secretion, thereby promoting vasoconstriction and reducing cerebral perfusion [47]. It is also reported that higher HOMA-IR was correlated with lower

Table 4
ROC and reclassification analyses for TyG to improve the risk stratification of moderate to severe cSVD.

Model	AUC (95%CI)	*P* value	*P* for comparison	IDI (95%CI)	*P* value
TyG	0.636(0.572,0.700)	< 0.001	–	–	–
Traditional risk factors *	0.745(0.692,0.794)	< 0.001	–	Reference	–
Traditional risk factors + TyG	0.802(0.752,0.846)	< 0.001	0.003	0.080(0.050,0.110)	< 0.001

Abbreviations: ROC: receiver operating characteristic curve; TyG: triglyceride-glucose index; cSVD, cerebral small vessel disease; AUC: area under the curve; 95% CI: 95% confidence interval; IDI: integrated discrimination index.

* Traditional risk factors: age, sex, current or former smoking, hypertension, history of stroke/transient ischemic attack, untreated dyslipidemia, untreated diabetes mellitus, homocysteine, uric acid.

CBF throughout the brain in middle-aged cognitively healthy adults [48] and mean gray-matter CBF in IR was 4.4 mL/100 g per minute lower than in healthy subjects [49]. Besides, IR can lead to vascular stiffness partly via enhanced SGK-1 signaling [50]. Increased vascular stiffness leads to fluid stagnation in perivascular spaces and impaired interstitial flushing, contributing to EPVS. Additionally, IR may enlarge the role of modifiable risk factors in cSVD. In our study, we observed a correlation between TyG index and BMI, DM, and uric acid. Therefore, IR may indirectly lead to cSVD via the elevation of risks above.

Early identification of the patients with a high risk of cSVD can help clinicians to adopt a rational treatment and prevention strategy timely to delay the cSVD progression. The results of ROC and IDI confirmed the added value of the TyG index on top of related medical history risk factors, such as DM and dyslipidemia, implicating the remarkable usefulness of TyG index to identify subjects with moderate to severe cSVD. TyG index is an index consisting of two risk factors for cSVD, lipid-related and glucose-related factors, making it probably more sensitive to the people at high risk of cSVD than DM and dyslipidemia alone. Moreover, the TyG index is a reliable alternative biomarker of IR, which can precede DM for several years. Additionally, IR is also a significant hallmark of many independent risk factors for cSVD, which have mentioned previously. By adding TyG index into clinical use, clinicians could better recognize the people at high risk of cSVD prior to the occurrence of the traditional cerebrovascular risk factors.

For a long time, the TG target is less restrictive in the primary and secondary prevention of cerebrovascular diseases [51,52], due to their debatable relationship [53]. However, unlike the ambiguous relationship between TG and cerebrovascular diseases, the associations between IR and cerebrovascular diseases and related risk factors are relatively definite. Previous studies have demonstrated that IR was associated with DM [33], hypertension [37], metabolic syndrome [54], atherosclerotic cardiovascular disease [26] and stroke [55]. Our study also indicated the important roles of TyG index in cSVD, reconfirming the important roles of IR in cSVD. As one of the independent risk factors of IR, TG plays a crucial role in IR [56]. On the one hand, increased TG levels can induce elevated free fatty acid levels and promote the increased flux of fatty acid from adipose tissue to non-adipose tissue, which could impair insulin signaling and contribute to IR. On the other hand, increased TG level can stimulate hepatic gluconeogenesis, promoting fasting and postprandial hyperglycemia through increased fatty acid delivery to the liver, which will increase the burden of islet B cell and results in IR over time [57]. Based on the role of TG in IR, it is maybe time for us to reconsider the importance of TG control in cerebrovascular diseases including cSVD.

Although our study widely discussed the role and value of TyG index in cSVD, it was subject to some caveats. First, this is a cross-sectional study with a medium sample in a memory clinic population. In the future, longitudinal studies are required to establish the causality and explore the predictive ability of TyG index in the progression of cSVD. Second, previous studies demonstrated that glucose-lowering or lipid-lowering agents might skew the conclusion [26]. Therefore, we excluded patients using glucose-lowering or lipid-lowering agents in our study, which may cause selection bias. In next, we need a larger sample to further confirm the reliability of the results. Third, laboratory parameters, especially the levels of fast glucose, were only measured once with a potential bias due to measurement error and physiologic variation. Forth, it is noticeable that this study only elucidated the relationship between TyG index and cSVD, and further work is needed to compare the predictive values of TG and FBG alone with TyG index in the future.

5. Conclusion

In conclusion, we demonstrated that TyG index is associated with the cSVD and could help to optimize the risk stratification of cSVD in a memory clinic population. We believe TyG index, as a simple and cost-effective marker of IR, may have the potential to be used in clinics in the future.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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