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ORIGINAL RESEARCH

Cerebral Small Vessel Disease is Associated with Mild Cognitive Impairment in Type 2 Diabetes Mellitus

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Objective: Type 2 diabetes mellitus (T2DM) is associated with cognitive impairment, but the underlying cerebral small vessel disease (CSVD)-related structural brain correlates are unclear. The aim of this study was to investigate the relationship between various imaging markers of CSVD and mild cognitive impairment (MCI) in patients with T2DM.

Methods: A total of 228 eligible participants with T2DM who were divided into MCI group and normal cognitive group based on neuropsychological assessment were enrolled in this retrospective study. White matter hyperintensity (WMH), lacunes, cerebral microbleeds (CMBs) and enlarged perivascular spaces (EPVS) were evaluated based on brain magnetic resonance imaging (MRI). The total CSVD burden score was calculated by combining the above four markers of CSVD. Binary logistic regression analysis was used to evaluate the relationship between different imaging markers of CSVD and MCI in patients with T2DM. Kruskal–Wallis test and Jonckheere–Terpstra test were used to compare mean MoCA scores among individuals with varying CSVD markers.

Results: In the multivariate binary logistic regression analyses, moderate or severe total CSVD burden (OR: 3.29, 95% CI: 1.63–7.38, P=0.004; OR: 10.97, 95% CI: 4.94–24.34, P<0.001, respectively), moderate dWMH (OR: 3.26, 95% CI: 1.43–7.41, P=0.005), extensive lacunes (OR: 4.97, 95% CI: 1.79–13.81, P=0.002), and moderate BG-EPVS (OR: 3.84, 95% CI: 1.81–8.13, P<0.001) were associated with MCI in patients with T2DM related to MCI after adjusting for potential confounders. There was a trend for significant decrease in MoCA scores with increase severity of dWMH, pWMH, lacunes, BG-EPVS, deep CMBs, or total CSVD burden (P for trend <0.05).

Conclusion: Different imaging markers of CSVD, particularly total CSVD burden, were associated with an increased risk of MCI and decline in MoCA scores in patients with T2DM. These findings may provide clues for future studies to explore early diagnostic imaging markers of cognitive impairment in relation to T2DM.

Keywords: type 2 diabetes mellitus, mild cognitive impairment, cerebral small vessel disease

Introduction

Type 2 diabetes mellitus (T2DM) is a highly prevalent disorder in middle or older population and a tremendous threat to global public health.[1] T2DM-induced cognitive impairment, including mild cognitive impairment (MCI) and dementia, has become a serious health problem worldwide.[2] People with T2DM have a 1.5–2.8-times increased risk of dementia compared with those without T2DM,[3,4] and a high proportion of patients (up to 20%) older than 60 years with T2DM might have dementia.[5] In particular, T2DM increases the risk of incident MCI[6,7] and accelerates the progression from MCI to dementia.[2,5,8] Moreover, cognitive impairment, especially dementia, may lead to poor self-management of T2DM, which in turn result in more cerebrovascular events and worse cognitive ability.[1] Given that early detection

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and interventions for cognitive impairment are conducive to diabetes care and self-management, it is critical to identify effective diagnostic markers of MCI in patients with T2DM.

Cerebral small vessel disease (CSVD) is a disorder of small perforating arterioles, capillaries and small veins of the brain.[9] Imaging markers of CSVD seen on neuroimaging include white matter hyperintensity (WMH), lacunes, cerebral microbleeds (CMBs) and enlarged perivascular spaces (EPVS).[10] CSVD is a prominent cause of cognitive impairment and an independent risk factor for MCI.[10,11] Total CSVD burden score, calculated by integrating above imaging markers, might better represent the severity of CSVD and predict cognitive impairment.[12] In addition, the presence of brain abnormalities on magnetic resonance imaging (MRI), particularly markers of CSVD, are more common in people with T2DM.[13,14] However, few studies have explored the association between different imaging markers of CSVD and MCI in patients with T2DM. In this study, we aimed to evaluate whether different imaging markers of CSVD (ie, total CSVD burden score, WMH, CMBs, lacunes, EPVS) are associated with an increased risk of MCI in patients with T2DM.

Participants and Methods

Study Population

This is a retrospective study of patients with T2DM who were hospitalized at Hebei General Hospital between October 2016 and October 2020 according to in-hospital records stored in electronic databases. Inclusion criteria for patients were as follows: (1) older than 50 years, (2) diagnosis of T2DM according to World Health Organization criteria,[15] and (3) have complete MRI sequences for evaluating different imaging markers of CSVD. We excluded those with symptomatic vascular events within 3 months, dementia and other conditions that may be associated with cognitive function, such as brain injuries, epilepsy, anxiety, depression, hypothyroidism, hyperthyroidism or carbon monoxide poisoning. Finally, we included 228 eligible patients in the study.

Clinical Assessment

The following data on demographic and clinical characteristics were collected in our study: age, gender, years of education, body mass index, duration of T2DM, and history of smoking, alcohol drinking, hypertension, coronary heart disease, and stroke. Body mass index was calculated as weight (kg) divided by the square of height (m^2). Hypertension was defined as blood pressure ≥140/90 mmHg, a previous diagnosis of hypertension, or treatment with antihypertensive drugs. Laboratory markers such as hemoglobin A1c (HbA1c), total cholesterol, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, serum total homocysteine and uric acid were evaluated after 8 hours of overnight fasting.

Brain MRI Data Acquisition and Evaluation

MRI examination was performed in all patients with 3.0 tesla magnetic resonance scanners (Signa, GE Healthcare, USA). The neuroimaging sequences included T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), fluid-attenuated inversion recovery (FLAIR) and susceptibility weighted imaging (SWI). Full details of MR scanning parameters have been described previously.[16]

Imaging markers of CSVD were assessed independently by two readers according to the standard published criteria.[10] In case of disagreement on any markers, a radiologist assessed the images in order to achieve consensus. All ratings were blinded to all patient data. WMH was displayed as hyperintensity on T2WI and FLAIR, without cavitation. The severity of periventricular WMH (pWMH) or the deep WMH (dWMH) was evaluated using Fazekas rating scale.[17] We categorized WMH as mild (0–1 score), moderate (2 score) and severe (3 score). A lacune was classified as a round or ovoid, subcortical cavity, between 3 and 15 mm in diameter, with a similar signal of cerebrospinal fluid on T1WI or T2WI, following the territory of a perforating arteriole.[10] The number of lacunes was recorded. The grades of lacunes were grouped as being absent, mild (1–3), extensive (≥4).[18] CMBs were defined as a small (2–10 mm in diameter) area of signal void on SWI and graded using the Microbleed Anatomical Rating Scale.[19] The number of CMBs in lobar or deep was recorded. EPVS was defined as a round or linear, cerebrospinal fluid filled cavity with a diameter generally smaller than 3 mm on all sequences and measured in two different regions: the basal ganglia (BG) and centrum semiovale (CSO). In line with previous studies,

EPVS in CSO or BG was rated on a semi-quantitative scale from 0 to 4 (0 = none, 1 = 1–10, 2 = 11–20, 3 = 21–40 and 4 = >40).[20] We categorized EPVS as mild (0–1 score), moderate (2 score) and severe (3–4 score). The total CSVD burden score was rated on an ordinal scale from 0 to 4. A point was awarded for each of the following: severe pWMH or moderate-to-severe dWMH, presence of lacune, any deep CMBs and moderate-to-severe EPVS in BG.[21–23] We categorized the total CSVD burden as mild (0–1 score), moderate (2 score) and severe (3–4 score).[24]

Cognitive Function Assessment

The diagnosis of MCI was made according to the established criteria recommended by National Institute on Aging and Alzheimer's Association workgroups.[25] The criteria included 1) concern regarding a change in cognition (patients or their families); 2) objective evidence of impairment in one or more cognitive domains, which in our study, was assessed by standardized translated version of Montreal Cognitive Assessment (MoCA) Beijing version (www.mocatest.org); 3) preservation of independence in functional abilities according to basic and instrumental activities of daily living (ADL); 4) absence of dementia. According to a previously published protocol, the normal MoCA score is >13 for illiterate, >19 for individuals with 1–6 years of education, and >24 for individuals with 7 or more years of education for Chinese adults.[26]

Statistical Analysis

Continuous variables were expressed as mean (standard deviation) or median (interquartile range) as appropriate and analyzed by Mann–Whitney *U*-test or *t* test. Categorical variables were presented with case (percentage) and analyzed by chi-square test. Ordinal variables, such as the severity of different imaging markers of CSVD, were analyzed by the Kruskal–Wallis test based on grouping. Multivariate binary logistic regressions were performed to determine whether different imaging markers of CSVD were independent risk factors for MCI in patients with T2DM. To assess the relationships between MoCA scores and different imaging markers of CSVD, Kruskal–Wallis test and Jonckheere–Terpstra test were used to compare mean MoCA scores among individuals with varying CSVD markers (total CSVD burden, WMH, CMBs, lacunes, and EPVS). All above statistical analyses were performed using SPSS software package 21.0 (IBM corporation, Armonk, NY). Values of $P<0.05$ were considered statistically significant.

Results

Participants Characteristics

This retrospective study included 228 eligible patients with T2DM. The characteristics of all participants are presented in Tables 1 and 2. The mean age of the participants was 67.4±8.1 years and 55.3% were male. Frequencies of different imaging markers of CSVD: moderate-to-severe dWMH [115 (50.4%)], moderate-to-severe pWMH [140 (61.4%)], lacunes [135 (59.2%)], lobar CMBs [60 (26.3%)], deep CMBs [68 (29.8%)], moderate-to-severe BG-EPVS [133 (58.4%)], moderate-to-severe CSO-EPVS [165 (72.4%)], and moderate-to-severe total CSVD burden [138 (60.5%)]. All individuals were divided into normal cognitive group (n = 104) and MCI group (n = 124). Patients with MCI were significantly older and showed more history of stroke than those without cognitive impairment ($P<0.05$, Table 1). The MCI group presented higher HbA1c and serum tHcy levels than normal cognitive group ($P<0.05$, Table 1). On MRI, the presence of MCI in patients with T2DM was associated with more severe dWMH, pWMH, lacunes, deep CMBs, BG-EPVS, and total CSVD burden ($P<0.05$, Table 2).

Different Imaging Markers of CSVD and MCI in Patients with T2DM

Multivariate binary logistic regressions were performed to determine the association between different imaging markers of CSVD and MCI in patients with T2DM, as shown in Table 3. The moderate or severe total CSVD burden was associated with MCI (odds ratio [OR]: 3.29, 95% confidence interval [CI]: 1.63–7.38, $P=0.004$; OR: 10.97, 95% CI: 4.94–24.34, $P<0.001$, respectively) after adjusting for age, education, history of stroke, HbA1c and serum tHcy (Model 2). The moderate dWMH (OR: 3.26, 95% CI: 1.43–7.41, $P=0.005$), extensive lacunes (OR: 4.97, 95% CI: 1.79–13.81, $P=0.002$), and moderate BG-EPVS (OR: 3.84, 95% CI: 1.81–8.13, $P<0.001$) were all related to MCI after

Table 1 Clinical Characteristics of All Participants with T2DM

Variable	Total (n = 228)	Normal Cognitive Group (n = 104)	MCI Group (n = 124)	*P* value
Age, mean (SD), years	67.4±8.1	65.6±8.3	68.8±7.6	0.002*
Sex (male), n (%)	126 (55.3)	54 (51.9)	72 (58.1)	0.353
Education, median (IQR), years	11 (9–12)	12 (9–12)	9 (9–12)	0.059
Body mass index, median (IQR), kg/m^2	25.1 (23.3–26.8)	25.01 (23.4–27.2)	25.1 (22.9–26.7)	0.912
Current smoking, n (%)	40 (17.5)	14 (13.5)	26 (21.0)	0.138
Alcohol use, n (%)	27 (11.8)	9 (8.7)	18 (14.2)	0.194
Hypertension, n (%)	262 (71.2)	72 (69.2)	96 (77.4)	0.162
Duration of T2DM, median (IQR), year	10 (4.3–15.0)	10.0 (4.3–14.8)	10.0 (4.3–15.0)	0.674
Coronary heart disease, n (%)	54 (23.7)	20 (19.2)	34 (27.4)	0.147
History of stroke	136 (37.0)	32 (30.8)	57 (46.0)	0.019*
HbA1c, median (IQR), %	7.1 (6.5–7.9)	6.9 (6.3–7.6)	7.2 (6.5–8.1)	0.021*
TC, median (IQR), mmol/L	4.30 (3.59–5.29)	4.34 (3.55–5.37)	4.26 (3.61–5.20)	0.557
TG, median (IQR), mmol/L	1.38 (1.00–2.09)	1.31 (0.99–2.02)	1.48 (1.00–2.13)	0.585
HDL-C, median (IQR), mmol/L	1.07 (0.92–1.29)	1.08 (0.94–1.28)	1.06 (0.90–1.30)	0.785
LDL-C, median (IQR), mmol/L	2.73 (2.14–3.47)	2.76 (2.14–3.65)	2.72 (2.15–3.37)	0.560
Uric acid, mean (SD), umol/L	301.2±83.6	310.0±84.9	293.9±82.2	0.150
Serum tHcy, median (IQR), umol/L	13.8 (11.4–16.6)	12.9 (10.6–15.7)	14.5 (11.7–17.0)	0.016*

Note: *Denotes signifcance at a *P* value of <0.05.

Abbreviations: SD, standard deviation; IQR, interquartile range; MCI, mild cognitive impairment; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; tHcy, total homocysteine.

Table 2 Characteristics of Imaging Markers of CSVD of All Participants with T2DM

Variable	Total (n = 228)	Normal Cognitive Group (n = 104)	MCI Group (n = 124)	*P* value
Severity of dWMH, n (%)				
Mild	113 (49.6)	75 (72.1)	38 (30.6)	<0.001*
Moderate	62 (27.2)	16 (15.4)	46 (37.1)	
Severe	53 (23.2)	13 (12.5)	40 (32.3)	
Severity of pWMH, n (%)				
Mild	88 (38.6)	57 (54.8)	31 (25.0)	< 0.001*
Moderate	79 (34.6)	32 (30.8)	47 (37.9)	
Severe	61 (26.8)	15 (14.4)	46 (37.1)	
Severity of lacunes, n (%)				
Absent	93 (40.8)	64 (61.5)	29 (23.4)	<0.001*
Mild	55 (24.1)	23 (22.1)	32 (25.8)	
Extensive	80 (35.1)	17 (16.3)	63 (50.8)	
No. of lobar CMBs, n (%)				
0	168 (73.7)	82 (78.8)	86 (69.4)	0.137
1	36 (15.8)	11 (10.6)	25 (20.2)	
≥2	24 (10.5)	11 (10.6)	13 (10.5)	
No. of deep CMBs, n (%)				
0	160 (70.2)	83 (79.8)	77 (62.1)	0.003
1	27 (11.8)	10 (9.6)	17 (13.7)	
≥2	41 (18.0)	11 (10.6)	30 (24.2)	
Severity of BG-EPVS, n (%)				
Mild	95 (41.6)	65 (62.5)	30 (24.2)	<0.001*
Moderate	85 (37.3)	24 (23.1)	61 (49.2)	
Severe	48 (21.1)	15 (14.4)	33 (26.6)	

(*Continued*)

Table 2 (Continued).

Variable	Total (n = 228)	Normal Cognitive Group (n = 104)	MCI Group (n = 124)	*P* value
Severity of CSO-EPVS, n (%)				
Mild	63 (27.6)	31 (29.8)	32 (25.8)	0.157
Moderate	93 (40.8)	46 (44.2)	47 (37.9)	
Severe	72 (31.6)	27 (26.0)	45 (36.3)	
Severity of total CSVD burden, n (%)				
Mild	90 (39.5)	66 (63.5)	24 (19.4)	<0.001*
Moderate	48 (21.0)	20 (19.2)	28 (22.6)	
Severe	90 (39.5)	18 (17.3)	72 (58.1)	

Note: *Denotes significance at a *P* value of <0.05.
Abbreviations: MCI, mild cognitive impairment; CSVD, cerebral small vessel disease; dWMH, deep white matter hyperintensity; pWMH, periventricular white matter hyperintensity; CMBs, cerebral microbleeds; BG-EPVS, basal ganglia-enlarged perivascular spaces; CSO-EPVS, centrum semiovale-enlarged perivascular spaces.

Table 3 Analysis of the Association Between Different Imaging Markers of CSVD and MCI in Patients with T2DM

Variable	Model 1		Model 2		Model 3	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Severity of dWMH						
Mild	Reference		Reference		Reference	
Moderate	5.01 (2.47–10.15)	<0.001*	4.61 (2.24–9.48)	<0.001*	3.26 (1.43–7.41)	0.005*
Severe	5.87 (2.74–12.56)	<0.001*	5.34 (2.36–12.07)	<0.001*	2.15 (0.75–6.20)	0.157
Severity of pWMH						
Mild	Reference		Reference		Reference	
Moderate	2.33 (1.21–4.48)	0.011*	1.97 (0.99–3.91)	0.053	0.82 (0.35–1.93)	0.655
Severe	5.39 (2.54–11.46)	<0.001*	4.66 (2.07–10.49)	<0.001*	1.29 (0.45–3.78)	0.633
Severity of lacunes						
Absent	Reference		Reference		Reference	
Mild	2.88 (1.41–5.88)	0.004*	2.72 (1.27–5.83)	0.01*	2.31 (0.99–5.35)	0.051
Extensive	8.43 (4.14–17.15)	<0.001*	9.84 (4.20–23.09)	<0.001*	4.97 (1.79–13.81)	0.002*
No. of deep CMBs						
0	Reference		Reference		Reference	
1	1.97 (0.83–4.68)	0.127	1.98 (0.81–4.87)	0.137	2.11 (0.73–6.06)	0.166
≥2	3.34 (1.52–7.31)	0.003*	3.32 (1.47–7.49)	0.004*	1.62 (0.59–4.53)	0.359
Severity of BG-EPVS						
Mild	Reference		Reference		Reference	
Moderate	5.02 (2.62–9.61)	<0.001*	4.69 (2.39–9.22)	<0.001*	3.84 (1.81–8.13)	<0.001*
Severe	4.01 (1.86–8.64)	<0.001*	3.68 (1.63–8.31)	0.002*	1.43 (0.54–3.78)	0.467
Severity of total CSVD burden						
Mild	Reference		Reference		-	-
Moderate	3.46 (1.63–7.38)	0.001*	3.29 (1.48–7.32)	0.004*	-	-
Severe	10.27 (5.06–20.84)	<0.001*	10.97 (4.94–24.34)	<0.001*	-	-

Note: *Denotes significance at a *P* value of <0.05. Results from binary logistic regression analysis. Model 1: adjusted for age and education. Model 2: adjusted for age, education, history of stroke, HbA1c and serum tHcy. Model 3: adjusted for age, education, history of stroke, HbA1c, serum tHcy and imaging markers of CSVD (ie, WMH, CMBs, lacunes, and EPVS).
Abbreviations: MCI, mild cognitive impairment; CSVD, cerebral small vessel disease; T2DM, type 2 diabetes mellitus; dWMH, deep white matter hyperintensity; pWMH, periventricular white matter hyperintensity; CMBs, cerebral microbleed; BG-EPVS, basal ganglia-enlarged perivascular spaces.

adjusting for age, education, history of stroke, HbA1c, serum tHcy and imaging markers of CSVD (ie, WMH, CMBs, lacunes, and EPVS) (Model 3). No significant correlations were found between other imaging markers of CSVD after adjusting for all confounders (Model 3), although they were significantly associated with MCI in Model 1.

Different Imaging Markers of CSVD and MoCA Scores in Patients with T2DM

Assessment of the relationship between MoCA scores and the burdens of different imaging markers of CSVD revealed a negative correlation between MoCA scores and the severity of dWMH ($P<0.001$, P for trend <0.001) and pWMH ($P<0.001$, P for trend <0.001). MoCA scores displayed a close relationship with the severity of lacunes ($P<0.001$, P for trend <0.001), BG-EPVS ($P<0.001$, P for trend <0.001), and number of deep CMBs ($P=0.007$, P for trend $=0.002$). There was a trend for significant decrease in MoCA scores with increase in total CSVD burden ($P<0.001$, P for trend <0.001). There was no association between MoCA scores and lobar CMBs ($P=0.552$, p for trend $=0.362$) and CSO-EPVS ($P= 0.093$, P for trend $=0.073$) (Figure 1).

Discussion

In this study, we investigated the association between individual imaging markers of CSVD, total CSVD burden and MCI in patients with T2DM. We found that moderate or severe total CSVD burden, moderate dWMH, extensive lacunes, and moderate BG-EPVS were associated with an increased risk of MCI in patients with T2DM after adjusting for potential confounders. In addition, the more severe imaging markers of CSVD (ie, total CSVD burden, WMH, lacunes, deep CMBs and BG-EPVS) were associated with lower MoCA scores in patients with T2DM. Taken together, these findings indicated that the severity of imaging markers of CSVD may be a potential biomarker of MCI in patients with T2DM. Moreover, our results may provide clues for future studies to explore early diagnostic imaging markers of cognitive impairment in patients with T2DM.

Although T2DM has been shown to increase the risk of cognitive impairment, the underlying mechanisms of this association are still uncertain.[5,27] Underlying mechanisms proposed to explain the association between T2DM and cognitive impairment include endothelial dysfunction, blood–brain barrier dysfunction, inflammation, and insulin resistance.[5,27–29] Interestingly, these mechanisms seem to be pivotal factors contributing to the pathogenesis and development of CSVD,[9,30,31] which is a prominent cause of cognitive impairment.[32] However, it should be noted that few studies have comprehensively explored the association between various CSVD components and cognitive dysfunction (particularly MCI) in relation to T2DM.

As suggested by previous studies, EPVS is an imaging marker of CSVD and an important component of the brain glymphatic system, which is known to be related to cognitive decline and dementia.[33,34] And there is increasing evidence that T2DM could impair the brain glymphatic system and consequently provoke the development of cognitive impairment.[35] A few recent studies have explored the association between EPVS and cognitive impairment in T2DM patients. Zhao et al suggested that subcortical EPVS is independently associated with cognitive impairment in patients with T2DM.[36] Nevertheless, another study indicated that BG-EPVS severity, rather than CSO-EPVS, may be a potential imaging biomarker of cognitive impairment in T2DM patients.[37] In this study, we also found BG-EPVS was associated with MCI after adjusting for potential confounders, which may provide further evidence for understanding the different pathologies between CSO-EPVS and BG-EPVS in patients with T2DM.

In line with the results of previous studies, we found that the severity of WMH or lacunes was associated with cognitive impairment in patients with T2DM.[38,39] Moreover, the increase in WMH volume[39,40] or integrity disruptions of WMH[41] was related to worse cognition such as processing speed and executive function in T2DM. However, those studies did not further separately distinguish WMH location (pWMH or dWMH) and degree of cognitive impairment (MCI or dementia), although it is suggested different WMH locations may have different effects on MCI.[42] More importantly, other markers of CSVD, such as CMBs or EPVS, were not discussed in those studies, although previous studies suggested that CMBs or EPVS may be involved in cognitive impairment in relation to T2DM.[37,43] In our study, we found that both dWMH and pWMH were associated with MCI in patients with T2DM after adjusting for age and education. Additionally, we observed weaker associations between MCI and the severity of dWMH or pWMH after further controlling history of stroke, HbA1c and serum tHcy. Of note, when other imaging markers of CSVD were taken

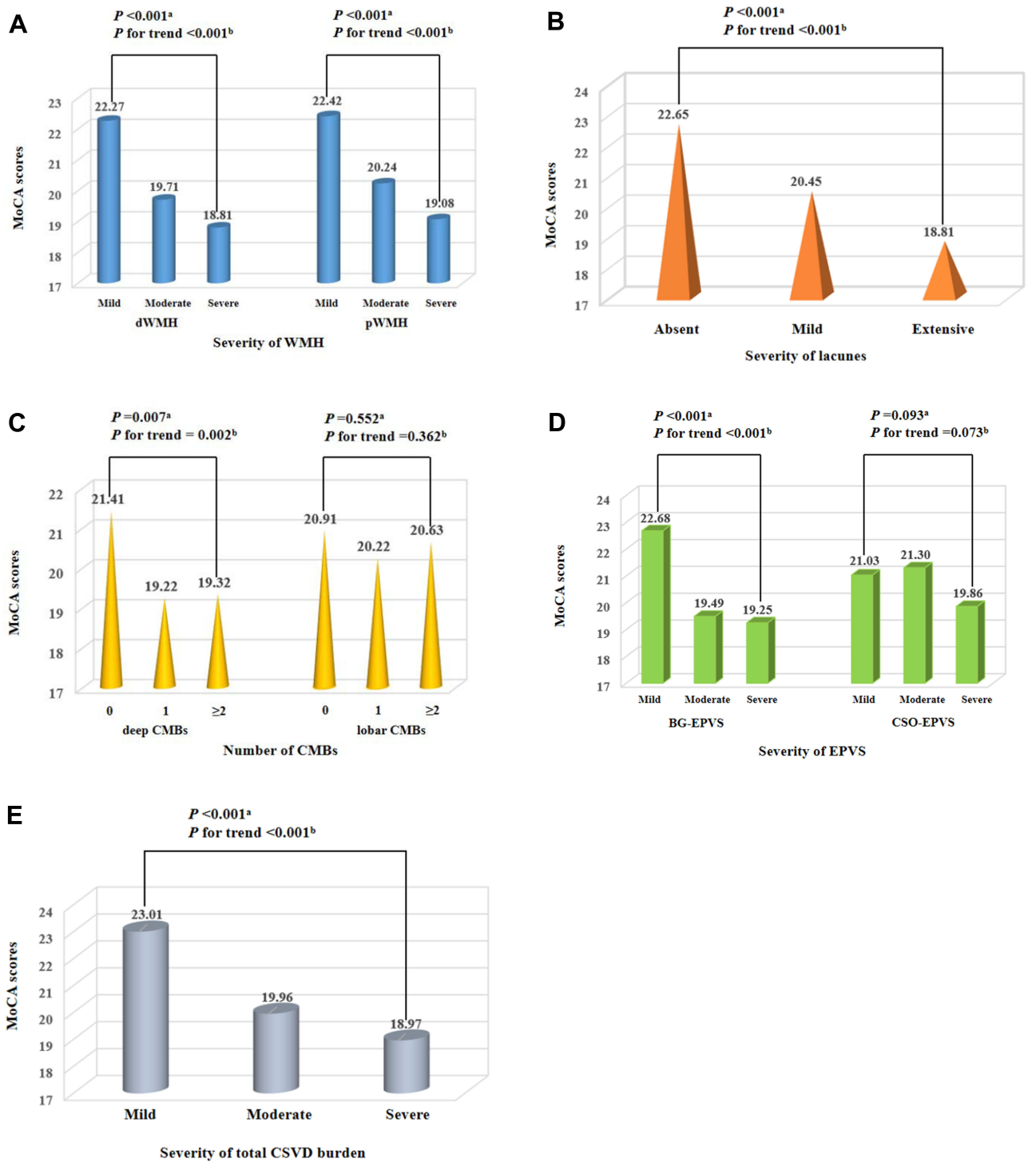

Figure 1 Distribution of mean values of MoCA scores according to WMH, lacunes, CMBs, EPVS and total CSVD burden. MoCA scores were negatively associated with the severity of WMH (both of dWMH and pWMH), lacunes, deep CMBs, BG-EPVS, and total CSVD burden ((**A**–**E**) respectively).

Notes: [a]Kruskal–Wallis test; [b]Jonckheere–Terpstra test.

Abbreviations: CSVD, cerebral small vessel disease; dWMH, deep white matter hyperintensity; pWMH, periventricular white matter hyperintensity; CMBs, cerebral microbleeds; BG-EPVS, basal ganglia-enlarged perivascular spaces; CSO-EPVS, centrum semiovale-enlarged perivascular spaces.

into account, the associations between MCI and pWMH or severe dWMH were not found in our study. Similar results were observed in our study between MCI and lacunes, CMBs, or EPVS, which suggested that there exist interactions among different imaging markers of CSVD.

In contrast to previous studies, an important strength of our study was that we assessed the association between total CSVD burden and MCI in patients with T2DM. To our knowledge, this is the first study to explore the association between total CSVD burden and MCI in the T2DM population. As mentioned above, there are interactions between various imaging markers of CSVD. Therefore, to better capture the overall effect of CSVD on the brain, a total CSVD burden score was mentioned and recommended in substantial literature.[12,21] Additionally, lines of evidence suggest that the total CSVD burden score may be a pragmatic and useful predictor of cognitive impairment in older people.[11,21] In the present study, we observed the severity of total CSVD burden was associated with MCI after adjustment for potential confounders, which suggested that total CSVD burden score may be a potential biomarker of MCI in patients with T2DM. In addition, we also found the severity of total CSVD burden was negatively associated with MoCA scores, which suggested that increased total CSVD burden may accelerate the progression of cognitive impairment, but this association requires more longitudinal studies to verify.

The main strength of our study is the detailed assessment of all components of CSVD, especially the total CSVD burden score. Another advantage is that the T2DM population with MCI, which is recognized as a transitional stage between normal cognition and dementia, was enrolled in our study. However, some limitations should be acknowledged in our study. Firstly, due to the cross-sectional design of this study, we were unable to investigate causality. Secondly, the study was conducted in a single center with a small sample size. Finally, other potential confounders, such as different antihyperglycemic drugs that may have an impact on cognitive impairment, were not taken into account. They may bias our analysis in the study. Future large prospective studies are needed to address these issues.

Conclusion

In summary, we found that different imaging markers of CSVD, especially total CSVD burden, were associated with MCI in patients with T2DM. In addition, we observed the severity of individual imaging markers of CSVD (ie, WMH, lacunes, deep CMBs and BG-EPVS) and total CSVD burden were negatively associated with MoCA scores. Our findings may provide clues for future studies to explore early diagnostic imaging markers of cognitive impairment in patients with T2DM.

Ethical Approval

The study followed the principles in the Declaration of Helsinki and was approved by the Ethical Committees of Hebei General Hospital (No. 2022051). We promised that the data of the participants were anonymized or maintained with confidentiality, and the rights or interests of participants were not invaded. Therefore, the requirement for informed consent in this study was waived in accordance with the national legislation and the institutional requirements.

Disclosure

The authors report no conflicts of interest in this work.

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