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Cerebral microbleeds: prevalence and relationship to clinical features in cognitive impairment with lewy body disease

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Abstract

Background The burden of cerebral microbleeds (CMBs) is greater in patients with dementia with Lewy bodies (DLB) than in those with Parkinson disease dementia (PDD), while few studies have been carried out in a large sample size, or focused on the prodromal stage. Thus, we investigated the clinical prevalence of CMBs and its relationship to clinical features in patients with DLB, PDD, mild cognitive impairment with Lewy bodies (MCI-LB) and Parkinson's disease with MCI (PD-MCI) in this study.

Methods In this retrospective multicenter cohort study, the study population consisted of 486 patients with DLB, 262 cases with PDD, 74 cases with MCI-LB and 107 cases with PD-MCI from 22 memory clinics between January 2018 and June 2022 in China. Demographic and clinical information were collected by reviewing medical records. CMBs were classified as "present" or "absent" in the Gradient Recalled-Echo or Susceptibility Weighted Imaging.

Results The prevalence of CMBs was significantly greater in patients with DLB with 24.69% (95% CI [20.92%, 28.78%]) than patients with PDD with 20.23% (95% CI [5.54%, 25.61%]), patients with MCI-LB with 16.22% (95% CI [8.67%, 26.61%]), and patients with PD-MCI with 12.15% (95% CI [6.63%, 19.88%]). There were sex and age differences in this prevalence. In all patients, the presence of CMBs was significantly and independently associated with the presence of visual hallucination (OR = 1.597, 95% CI [1.014, 2.517], $p = 0.044$) and fluctuating cognition (OR = 1.707, 95% CI [1.140, 2.556], $p = 0.009$); and it was associated with the severity of hallucination (B = 0.775, SE = 0.368, $p = 0.036$) and disinhibition (B = 0.363, SE = 0.148, $p = 0.014$) reflected by NPI. Moreover, CMBs in DLB were associated with the presence of parkinsonism symptoms (OR = 1.821, 95% CI [1.001, 3.314], $p = 0.05$), and the scores of UPDRS-III (B = 4.711, SE = 1.939, $p = 0.016$) and Hoehn-Yahn stage (B = 0.452, SE = 0.165, $p = 0.007$).

Conclusion Patients with DLB had a higher proportion of CMBs than PDD, MCI-LB and PD-MCI. CMBs in all DLB, PDD, MCI-LB and PD-MCI cases were associated with the presence of visual hallucination and fluctuating cognition; in DLB were associated with motor function.

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Keywords Cerebral microbleeds, Lewy body disease, Mild cognitive impairment, Dementia, Cerebral small vascular disease

Background

Lewy body dementia, which is comprised of dementia with Lewy bodies (DLB) and Parkinson disease dementia (PDD), is characterized by alpha-synuclein (α-Syn) deposition [1]as well as accompanied by other pathologies such as amyloid [2, 3], tau [4] and vascular pathology [5]. Several types of vascular pathology, including microinfarcts, atherosclerosis, white matter hyperintensities (WMH), and cerebral microbleeds (CMBs), are more common in DLB than in healthy controls or Alzheimer's disease (AD). Among these, the higher frequency of CMBs in DLB may contribute to the overall increased vascular burden in these patients [6–8].

CMBs are small, round or quasi-round, homogeneous lesions with clear boundaries and black or low signal areas on T2-weighted gradient recalled echo (GRE) or susceptibility weighted imaging (SWI) sequences. They usually occur in the lobar (cortical or subcortical), deep (basal ganglia, thalamus, internal capsule, external capsule, corpus callosum or deep/periventricular white matter) or infratentorial (brainstem or cerebellum) [9]. The estimated prevalence of CMBs is highly variable with 17–45% of cases of DLB [10, 11], and growing evidence has pointed that patients with DLB have an increased prevalence of CMBs compared to healthy controls and patients with PD [7], but broadly similar to or slightly higher than patients with AD [8, 12]. Little clinical study reported 24.2% [13] or 25.0% [14] of patients with DLB in early stage having CMBs. The presence and heavier burden of CMB can significantly increase the risk of intracerebral haemorrhage and ischaemic stroke in general population and dementia cases [15, 16]. Chen et al. found the presence of microbleeds, especially a higher number of CMBs, could worsen the cognitive function of PD and result in dementia [17]. One study also reported that the increased number of CMB was associated with cognitive impairment rather than neuropsychiatric symptoms or motor dysfunction at onset of DLB [8]. Although there were remaining other insights into the same content in some studies [18], all these findings reflect that CMBs may link to adverse clinical outcomes such as increased mortality and disability, cerebrovascular disease, cognitive or motor impairment [19, 20].

However, compared with the Lewy body dementia, very little is known about the prevalence of CMBs in their mild cognitive impairment (MCI) stage and the potential mechanism responsible for clinical features in mild cognitive impairment with Lewy bodies (MCI-LB) and Parkinson's disease with MCI (PD-MCI). In the present study, we compare the prevalence rates of CMBs in MCI-LB, PD-MCI, DLB and PDD, and examined the relationship between the presence of CMBs with the core clinical symptoms, cognitive function, motor function and behavioral and psychological symptoms in dementia (BPSD). This study may help to illustrate the clinical implications of CMBs in terms of prognoses and multiple clinical features in MCI-LB, PD-MCI, DLB and PDD.

Methods

Study design and participants

This study is a secondary analysis based on an ongoing multicenter cohort study in China. Information in current study was recorded in 22 memory clinics from 12 provinces from January 2018 to June 2022 by the China Lewy Body Disease Collaborative Alliance [21] (eAppendix 1). As the flowchart shown in Fig. 1, a total of 1183 medical records diagnosed with probable DLB ($n=486$), PDD ($n=262$), MCI-LB ($n=74$) and PD-MCI ($n=107$) were collected, since 78 patients with "uncertain diagnosis", 60 patients with incomplete demographic information, and 116 patients lacking of MRI information, they were excluded, finally leaving 929 eligible patients with MRI information for inclusion in the analysis.

All eligible patients had complete information of demographics, cardiometabolic conditions, four core clinical features (fluctuating cognition [22], visual hallucinations [23], parkinsonism [24], and Rapid eye movement sleep behavior disorder (RBD) [25]), and global cognition assessments (Mini-Mental State Examination (MMSE) [26], Montreal Cognitive Assessment (MoCA) [27], the Activities of daily living (ADL) [28], and the Clinical Dementia Rating (CDR) [29]). And 456 patients were assessed for BPSD using the Neuropsychiatric Inventory (NPI) [23]; 597 eligible patients were assessed for the severity of motor symptoms by Unified Parkinson's Disease Rating Scale-Part III (UPDRS-III) and Hoehn-Yahn stage; and 292 eligible patients were detected Apolipoprotein E (*APOE*) genotype.

Cardiometabolic conditions were defined according to our previous studies [30, 31]. Hypertension was defined as an individual with an average systolic blood pressure ≥ 140 mmHg or an average diastolic blood pressure ≥ 90 mmHg on ≥ three occasions, or patients taking antihypertensive drugs. Diabetes mellitus was defined as an individual having a fasting serum glucose level ≥ 7 mmol/L, a non-fasting serum glucose level ≥ 11.1 mmol/L, or using hypoglycemic agents. Heart disease in this study was defined as coronary atherosclerotic heart disease, which meant heart disease caused by coronary artery stenosis or occlusion. Stroke was defined as having

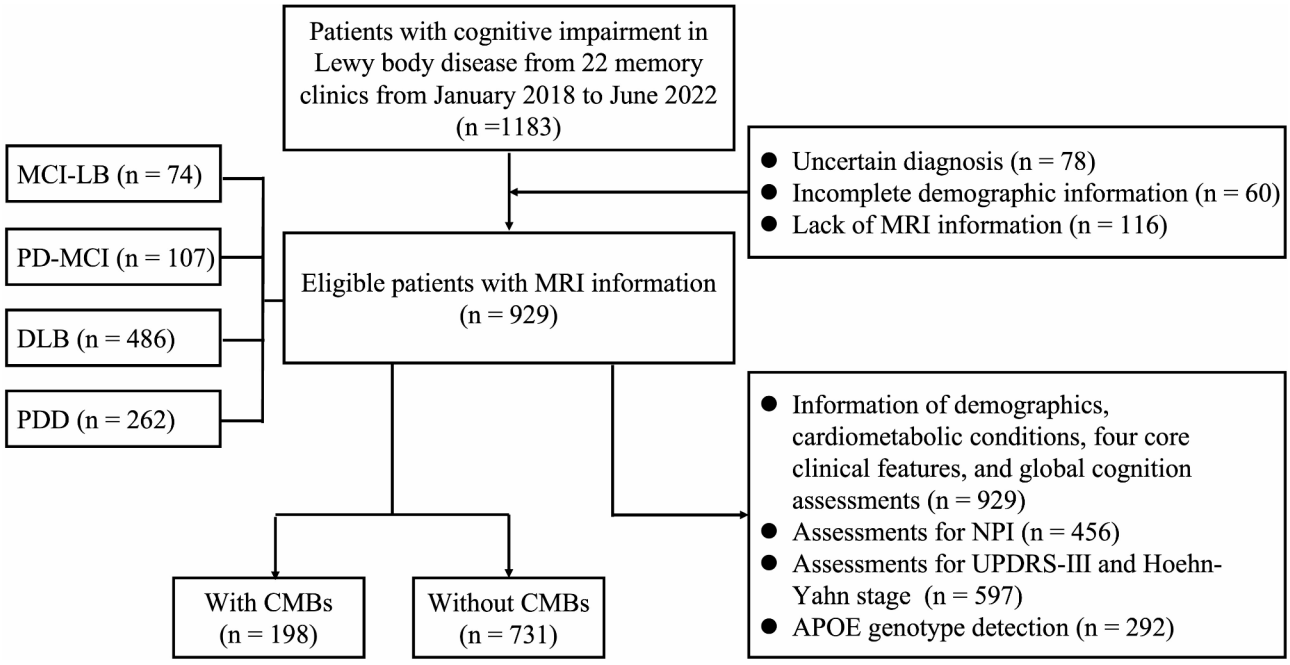

Fig. 1 Flowchart. MCI-LB, mild cognitive impairment with Lewy bodies; PD-MCI, Parkinson's disease with mild cognitive impairment; DLB, dementia with Lewy bodies; PDD, Parkinson's disease dementia; MRI, magnetic resonance imaging; NPI, the Neuropsychiatric Inventory; UPDRS-III, Unified Parkinson's Disease Rating Scale-Part III; APOE, Apolipoprotein E; CMBs, cerebral microbleeds

a diagnosed or a known history of hemorrhagic or ischemic stroke. A smoker was defined as an individual with a history of smoking ≥ 5 cigarettes per day for > 2 years. An alcohol drinker was defined as an individual with a history of drinking an alcoholic beverage ≥ 1 time per week for > 2 years [21]. The detailed methods of neuropsychiatric assessments and motor function assessment, as well as *APOE* detection were described in the previous articles [21, 32].

The diagnosis of MCI-LB, PD-MCI, DLB and PDD were according to their respective criteria [1, 33–36], and confirmed by two experienced neurologists according to their clinical information retrospectively, double-blindly. Those cases that did not reach a concordant diagnosis were classified as "uncertain diagnosis".

The Ethics Committees of the 22 centers approved all research activities in this multicenter study and waived informed consent because the data were pseudonymized from registers. The procedures were performed in accordance with the ethical standards of the Committee on Human Experimentation.

Imaging acquisition

MRI parameters and visual rating

The multicenter nature of this study and the various clinical setups did not allow standardization of sequences. The most frequently sequences performed were 3D T1WI, T2-FLAIR, GRE or SWI. MRI scans were performed on 3.0 Tesla scanners from Siemens (Magnetom TrioTim, Magnetom Skyra or Magnetom Prisma; Erlangen, Germany), General Electric (DISCOVERY MR750, Signa HDx; Milwaukee, WI, USA) and Philips (Ingenia and Achieva TX; Best, The Netherlands) using their standardized scanners sequence protocol respectively in different centers, and schematic representations of CMBs on part of scanners were displayed in Supplementary Fig. 1.

We visually assessed the presence of CMB, the visual rating scores of Fazekas scale and medial temporal lobe atrophy (MTA). The CMBs were defined as round or quasi-round areas with clear boundaries and black or low signal areas with a diameter of 2–10 mm in the GRE or SWI [37]. White matter hyperintensities (WMHs) were rated on T2-FLAIR sequences using the Fazekas scale, with a degree from 0 to 3. The MTA scale scores the degree of atrophy from 0 to 4 in the hippocampus, parahippocampal gyrus, entorhinal cortex and the surrounding cerebrospinal fluid spaces. The reconstruction mode and the degree of the MRI visual rating scales were used as described in our previous study, and all of the MRI readings were reviewed by two experienced neuroradiologists double-blindly [32, 38].

Amyloid B (Aβ) deposition and tau aggregation rating

Acquisition procedures for Aβ-PET and tau-PET have been fully described in a previous study [39, 40]. Briefly, the 3D Aβ-PET images were acquired by a Discovery Elite scanner (GE Healthcare) at Beijing Tiantan Hospital or a

Siemens Biograph 64 PET/CT scanner at PET center of Huashan Hospital. Patients were diagnosed as PIB-positive (at Shanghai Huashan Hospital) or AV45-positive (at Beijing Tiantan Hospital or Shanghai Huashan Hospital) on the basis of both visual interpretations of elevated binding in the neocortex and semiquantitative assessment with standardized uptake value ratio (SUVR) > 1.40 or SUVR > 1.11, respectively. [18 F]PM-PBB3 ([18 F]-APN-1607) PET scans were obtained on a Siemens Biograph 64 PET/CT system (Siemens, Erlangen, Germany) in 3D mode at Shanghai Huashan Hospital. A regional z score ≥ 2 was considered to define positive findings for semiquantitative interpretation at the regional level [41, 42].

Statistical analyses

In current study, the prevalence rates are expressed as proportions (%) and their 95% CIs. Demographic and clinical characteristics were described as the median (IQR) for continuous variables, or number of cases and proportions (n, %) for categorical variables. Binary and multiple groups comparisons were performed using chi-squared tests. For continuous variables, the Mann-Whitney U test and the Kruskal-Wallis test were performed for comparisons, and the P'-values were corrected by Bonferroni correction when comparing among the multiple groups according to the diagnoses (MCI-LB, DLB, PD-MCI, and PDD).

Statistically significant indicators in univariate analysis (Table 1) were included in multivariate analysis. And the Crude model, Model 1 (with correction for age at last visit, sex, history of hypertension, type-2 diabetes (T2DM), heart disease, stroke, and the habits of smoking and/or alcohol consumption), and Model 2 (with correction for Model 1 + scores of MTA-max and Fazekas) were applied in binary logistic regressions and linear regressions analysis, which were performed to calculate the associations between the presence of CMBs and clinical features. In all linear regression models, the normally distributed residuals and VIF diagnostics were perform, and almost all continuous variables were normally distributed, thus, the main results were expressed by "OR (95% CIs)" or "B ± standard error".

The IBM SPSS for Windows (version 25.0; IBM Corporation, Armonk, NY, USA) was used for statistical analyses, with $p < 0.05$ considered significant at the two-tailed α level.

Results

Demographic and clinical characteristics

Demographics and clinical characteristics of 929 patients are presented in Table 1, there were 198 patients had CMBs [122 (61.61%) men; the median age (Interquartile range, IQR): 71.50 (66.00, 77.00)], and 731 patients didn't have CMBs [332 (45.42%) men; the median age (IQR): 69.00 (64.00, 76.00)]. It indicates that no statistically significant differences were found in education, course of disease, the presence of visual hallucination, parkinsonism and RBD, the scores of UPDRS-III, Hoehn-Yahn stage and part of NPI-subitems between patients/CMBs (+) group and patients/CMBs (-) group. Compared to patients without CMBs, the patients with CMBs were older [71.50 (66.00, 77.00) vs. 69.00 (64.00, 76.00), $p = 0.003$] and more men (61.62% vs. 45.42%, $p < 0.001$); had higher proportions of hypertension (47.98% vs. 27.50%, $p < 0.001$), T2DM (30.30% vs. 8.76%, $p < 0.001$), heart disease (33.84% vs. 8.62%, $p < 0.001$), stroke (28.79% vs. 10.67%, $p < 0.001$), habits of smoking (44.44% vs. 10.26%, $p < 0.001$) and/or alcohol consumption (32.83% vs. 8.34%, $p < 0.001$); had higher scores of Fazekas ($p < 0.001$) and MTA (both sides, $p < 0.001$); performed worse cognitive function reflecting by MMSE ($p = 0.013$), MoCA ($p = 0.012$), ADL ($p = 0.003$), CDR ($p = 0.017$), and more severe BPSD reflecting by NPI ($p = 0.013$).

We also described the demographics and clinical characteristics of MCI-LB, PD-MCI, DLB and PDD in Supplementary Table 1. We found that patients with DLB were older, with longer course of disease, more *APOE* ε4 carriers, and had poorer cognitive performance or more severe BPSD reflecting by NPI than patients with MCI-LB, PD-MCI and PDD.

The prevalence of CMBs in Lewy body disease with cognitive impairment

With respect to the MRI images, the overall prevalence of CMBs in Lewy body disease with cognitive impairment was 21.31% (95% CI [18.67%, 23.95%]). The prevalence of CMBs was 16.22% (95% CI [8.67%, 26.61%]) in MCI-LB, 24.69% (95% CI [20.92%, 28.78%]) in DLB, 12.15% (95% CI [6.63%, 19.88%]) in PD-MCI, and 20.23% (95% CI [15.54%, 25.61%]) in PDD (Fig. 2).

As shown in Table 2, the male patients with MCI-LB (30.77% vs. 8.33%, $p = 0.012$) or DLB (32.29% vs. 18.25%, $p < 0.001$) showed higher prevalence of CMBs than female patients. Also, the prevalence of CMBs increased with age in PDD (12.24% in < 65 years old group, 23.53% in 65–70 years old group, 26.04% in > 70 years old group, $p = 0.043$). While there was no significant difference of the prevalence of CMBs in different educational subgroup.

The analysis of CMBs according to *APOE* ε4 allele, Aβ deposition and tau aggregation were shown in Supplementary Tables 2, and it revealed that the frequency of CMBs was significantly higher in patients with *APOE* ε4 allele than in those without (34.04% vs. 21.71%, $p = 0.018$), whereas it did not differ in Aβ-subgroups and tau-subgroups.

Table 1 Clinical characteristics of patients with and without CMB

Characteristics	Without CMBs (*n* = 731)	CMBs (*n* = 198)	Z/ x^2	*P*-value
Age at last visit, yrs	69.00 (64.00, 76.00)	71.50 (66.00, 77.00)	-2.922	0.003
Sex			16.361	< 0.001
Men	332 (45.42%)	122 (61.62%)		
Women	399 (54.58%)	76 (38.38%)		
Education, yrs	9.00 (6.00, 12.00)	9.00 (6.00, 12.00)	-0.159	0.874
Course of disease, yrs	2.00 (1.00, 3.00)	3.00 (2.00, 4.00)	-1.811	0.070
Hypertension	201 (27.50%)	95 (47.98%)	30.109	< 0.001
T2DM	64 (8.76%)	60 (30.30%)	62.545	< 0.001
Heart disease	63 (8.62%)	67 (33.84%)	82.338	< 0.001
Stroke	78 (10.67%)	57 (28.79%)	41.176	< 0.001
Smoking	75 (10.26%)	88 (44.44%)	125.846	< 0.001
Alcohol consumption	61 (8.34%)	65 (32.83%)	79.664	< 0.001
Fazekas	1.00 (1.00, 1.00)	1.00 (1.00, 2.00)	-5.860	< 0.001
MTA-left	1.00 (1.00, 1.00)	1.00 (1.00, 2.00)	-4.206	< 0.001
MTA-right	1.00 (1.00, 1.00)	1.00 (1.00, 2.00)	-4.385	< 0.001
MTA-max	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)	-4.125	< 0.001
Clinical core features	*n* = 731	*n* = 198		
Visual hallucinations	500 (68.40%)	145 (73.23%)	1.714	0.190
Fluctuating cognition	353 (48.29%)	119 (60.10%)	8.696	0.003
Parkinsonism	560 (76.61%)	150 (75.76%)	0.062	0.803
RBD	415 (56.77%)	111 (56.06%)	0.032	0.858
Motor function	*n* = 469	*n* = 128		
UPDRS-III	7.00 (0.00, 24.00)	10.50 (0.00, 23.75)	-0.038	0.970
Hoehn-Yahn stage	1.00 (0.00, 2.00)	1.25 (0.00, 2.00)	-0.146	0.884
0.0	170 (36.25%)	48 (37.5%)	4.371	0.730
1.0	80 (17.06%)	16 (12.50%)		
1.5	38 (8.10%)	11 (8.59%)		
2.0	95 (20.26%)	30 (23.44%)		
2.5	16 (3.41%)	2 (1.56%)		
3.0	51 (10.87%)	18 (14.06%)		
4.0	15 (3.20%)	3 (2.34%)		
5.0	4 (0.85%)	0 (0.00%)		
Cognitive function	*n* = 731	*n* = 198		
MMSE	20.00 (14.00, 24.00)	17.00 (13.00, 23.00)	-2.492	0.013
MoCA	13.00 (8.00, 18.00)	12.00 (7.00, 17.00)	-2.520	0.012
ADL	25.00 (21.00, 34.00)	29.00 (22.00, 38.00)	-2.959	0.003
CDR	1.00 (1.00, 2.00)	2.00 (1.00, 2.00)	-2.384	0.017
Behavioral and psychological symptoms	*n* = 347	*n* = 109		
Total-NPI scores	8.00 (2.00, 18.00)	14.00 (4.00, 21.50)	-2.486	0.013
Delusions	114 (32.85%)	47 (43.12%)	3.827	0.050
Hallucinations	260 (74.93%)	89 (81.65%)	2.088	0.148
Agitation	86 (24.78%)	33 (30.28%)	1.297	0.255
Depression	133 (38.33%)	51 (46.79%)	2.467	0.116
Anxiety	117 (33.72)	47 (43.12%)	3.184	0.074
Euphoria	20 (5.76%)	13 (11.93%)	4.693	0.030
Apathy	129 (37.18%)	45 (41.28%)	0.593	0.441
Disinhibition	32 (9.22%)	22 (20.18%)	9.547	0.002
Irritability	107 (30.84%)	50 (45.87%)	8.306	0.004
Aberrant motor behavior	94 (27.09%)	42 (38.53%)	5.189	0.023

Table 1 (continued)

Characteristics	Without CMBs (*n* = 731)	CMBs (*n* = 198)	Z/ x^2	*P*-value
Night-time behavior disturbances	89 (25.65%)	25 (22.94%)	0.141	0.707
Appetite and eating abnormalities	93 (43.87%)	48 (59.26%)	0.326	0.568

Since all of the continuous variables did not follow a normal distribution, we described them as the median (interquartile range, IQR). And categorical variables were described as number of cases and proportions (n, %) in this table. Comparisons between the two groups were performed using chi-squared tests for categorical variables, and Mann–Whitney U-test for continuous variables

CMBs, cerebral microbleeds; T2DM, type 2 diabetes mellitus; MTA, medial temporal lobe atrophy; RBD, rapid eye movement sleep behavior disorder; UPDRS-III, Unified Parkinson's Disease Rating Scale-Part III; MMSE, the Mini-Mental State Examination; MoCA, the Montreal Cognitive Assessment; ADL, the Activity of Daily Living Scale; CDR, the clinical dementia rating; NPI, the Neuropsychiatric Inventory

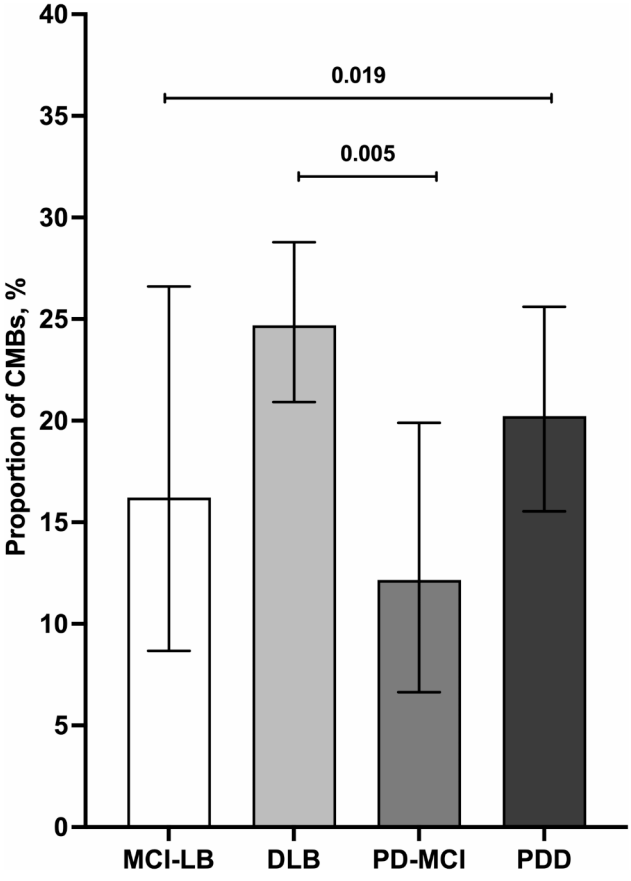

Fig. 2 The prevalence of CMBs in Lewy body disease with cognitive impairment. The prevalence of CMBs in MCI-LB, DLB, PD-MCI and PDD were shown by proportions (column) with 95%CI (error bars), and there was significant difference among the four groups ($p = 0.019$). When the four groups were compared separately, the prevalence of CMBs was significantly higher in the DLB group than in the PD-MCI group after Bonferroni correction ($p = 0.005$). CMBs, cerebral microbleeds; MCI-LB, mild cognitive impairment with Lewy bodies; PD-MCI, Parkinson's disease with mild cognitive impairment; DLB, dementia with Lewy bodies; PDD, Parkinson's disease dementia

Associations between CMBs and clinical characteristics

Logistic and linear regression analyses were also performed to investigate the association between CMBs and clinical characteristics. We found that the presence of fluctuating cognition, scores of MMSE, MoCA, ADL, CDR, and total-NPI were significantly associated with the presence of CMBs. After adjusting for all confounders, the presence of CMBs was significantly and independently associated with the presence of visual hallucination (OR = 1.597, 95% CI [1.014, 2.517], $p = 0.044$) and fluctuating cognition (OR = 1.707, 95% CI [1.140, 2.556], $p = 0.009$) in Table 3; whereas it was not significantly associated with the scores of UPDRS-III, Hoehn-Yahn stage, MMSE, MoCA, ADL or CDR in all eligible patients (Table 4). Moreover, the presence of CMBs can increased the presence of hallucination (OR = 2.175, 95% CI [1.036, 4.564], $p = 0.040$), depression (OR = 1.825, 95% CI [1.002, 3.324], $p = 0.049$) and night-time behavior disturbances (OR = 2.165, 95% CI [1.107, 4.234], $p = 0.024$) in adjusted model (Supplementary Table 3), and it was associated with the severity of hallucination (B = 0.775, SE = 0.368, $p = 0.036$) and disinhibition (B = 0.363, SE = 0.148, $p = 0.014$) reflected by NPI (Table 4).

CMBs in DLB were associated with the presence of parkinsonism (OR = 1.821, 95% CI [1.001, 3.314], $p = 0.05$), and the scores of UPDRS-III (B = 4.711, SE = 1.939, $p = 0.016$) and Hoehn-Yahn stage (B = 0.452, SE = 0.165, $p = 0.007$) (Supplementary Table 4). While these findings were not significant in patients with MCI-LB, PD-MCI and PDD, respectively (Supplementary Tables 5–7).

Discussion

This study showed that CMBs are common in patients with DLB, PDD, MCI-LB and PD-MCI. Approximately a quarter of patients with DLB had CMBs (24.69%), which was similar in PDD (20.23%) and MCI-LB (16.22%) but significantly higher than PD-MCI (12.15%). Moreover, CMBs in these cases were associated with the presence of visual hallucination and fluctuating cognition; in DLB were associated with motor function.

To our knowledge, this is the first study in a large sample to report the prevalence rates of CMBs in MCI-LB, PD-MCI, DLB and PDD. We observed the prevalence of CMBs in DLB and PDD was in keeping with previous studies [10, 11], though Kim et al. [7]. reported a slightly higher prevalence of CMBs in patients with DLB (19/42, 45.2%) and PDD (23/88, 26.1%). And in a previous neuropathologic study, a higher proportion of CMBs (75%) was reported due to the very small sample size (eight

Table 2 The prevalence of CMBs in lewy body disease with cognitive impairment subgrouped by sex, age and educational level

Diagnosis	Subgroups	Num. of cases (With CMBs/Without CMBs)	Prevalence	95% CI		*P*-value
				Lower bound	Upper bound	
MCI-LB	Men	8/18	30.77%	14.33%	51.79%	0.012
	Women	4/44	8.33%	2.32%	19.98%	
DLB	Men	72/151	32.29%	26.20%	38.85%	< 0.001
	Women	48/215	18.25%	13.77%	23.46%	
PD-MCI	Men	9/58	13.43%	6.33%	23.97%	0.599
	Women	4/36	10.00%	2.79%	23.66%	
PDD	Men	35/105	23.91%	17.07%	31.91%	0.117
	Women	20/104	16.13%	10.14%	23.81%	
MCI-LB	<65 years old	1/6	14.29%	0.36%	57.87%	1.000
	65–70 years old	6/31	16.22%	6.19%	32.01%	
	>70 years old	5/25	16.67%	5.64%	34.72%	
DLB	<65 years old	16/63	20.25%	12.04%	30.80%	0.502
	65–70 years old	32/84	27.59%	19.70%	36.66%	
	>70 years old	72/219	24.74%	19.89%	30.11%	
PD-MCI	<65 years old	6/43	12.24%	4.63%	24.77%	0.868
	65–70 years old	5/30	14.29%	4.81%	30.26%	
	>70 years old	2/21	8.70%	1.07%	28.04%	
PDD	<65 years old	12/86	12.24%	6.49%	20.41%	0.043
	65–70 years old	16/52	23.53%	14.09%	35.38%	
	>70 years old	25/71	26.04%	17.62%	36.00%	
MCI-LB	No formal education	2/20	9.09%	1.12%	29.16%	0.385
	Primary school	5/14	26.32%	9.15%	51.20%	
	Junior high school or above	5/28	15.15%	5.11%	31.90%	
DLB	No formal education	9/38	19.15%	9.15%	33.26%	0.372
	Primary school	30/73	29.13%	20.59%	38.90%	
	Junior high school or above	81/255	24.11%	19.63%	29.05%	
PD-MCI	No formal education	1/0	100.00%	2.50%	100.00%	1.000
	Primary school	2/14	12.50%	1.55%	38.35%	
	Junior high school or above	10/80	11.11%	5.46%	19.49%	
PDD	No formal education	3/26	10.34%	2.19%	27.35%	0.402
	Primary school	13/49	20.97%	11.66%	33.18%	
	Junior high school or above	37/134	21.64%	15.72%	28.57%	

CMBs, cerebral microbleeds; 95% CIs, 95% confidential intervals; MCI-LB, mild cognitive impairment with Lewy bodies; PD-MCI, Parkinson's disease with mild cognitive impairment; DLB, dementia with Lewy bodies; PDD, Parkinson's disease dementia

patients with DLB) [43]. In our study, CMBs were present in 16.22% of the patients with MCI-LB. Van de Beek et al. [14] and Mendes et al. [13] provided the first two clinical studies in patients with prodromal DLB, and reported 24%~25% of them had CMBs. Using the same approach, there were 197 patients with DLB in prodromal and mild stage (74 patients with MCI-LB and 123 patients with mild DLB) in our study, and 42 (21.32%) patients of them had CMBs, which was similar to previous finding. Additionally, we found 12.15% (13/107) patients with PD-MCI having CMBs in current study. Literatures has revealed 11 – 20% patients with PD had CMBs, moreover, the occurrence of CMBs may worsen the cognitive function of patients with PD and result in dementia [17, 20], also associated with poor cognitive performance in PDD [44]. Unfortunately, no research has focused on the occurrence of CMBs in patients with PD-MCI.

In this study, microbleeds in DLB and MCI-LB were male predominance, which is in keeping with previous studies [6, 45, 46]. Compared with women, men have earlier or more Aβ deposition and a higher proportion of cerebrovascular risk factors (e.g., hypertension, cardiovascular disease, smoking and alcohol consumption, higher body mass index), which would increase hemorrhage risk [47, 48]. We also found that the prevalence of CMBs in PDD increased with age. CMB may be understood as part of the ageing process [49], and the prevalence of hypertension, stroke, obstructive sleep apnea, and other pathologies increases with ageing, which all contribute to CMBs occurrence [50]. Our findings reported that the prevalence of CMBs was significantly

Table 3 Associations between the presence of CMBs and clinical core features in all cases

Clinical core feature		Crude					Model 1					Model 2				
		B	SE	OR	95%CI	*P*	B	SE	OR	95%CI	*P*	B	SE	OR	95%CI	*P*
Visual hallucinations	Constant	0.772	0.080	2.165		< 0.001	-1.899	0.678	0.150		0.005	-1.775	0.695	0.170		0.011
	CMB	0.234	0.179	1.264	0.890 ~ 1.796	0.191	0.654	0.225	1.924	1.238 ~ 2.990	0.004	0.468	0.232	1.597	1.014 ~ 2.517	0.044
Fluctuating cognition	Constant	-0.068	0.074	0.934		0.355	-1.314	0.623	0.269		0.035	-1.17	0.63	0.310		0.063
	CMB	0.478	0.163	1.613	1.172 ~ 2.220	0.003	0.653	0.201	1.921	1.296 ~ 2.846	0.001	0.535	0.206	1.707	1.140 ~ 2.556	0.009
Parkinsonism	Constant	1.186	0.087	3.275		< 0.001	5.951	0.820	384.224		< 0.001	6.017	0.825	410.189		< 0.001
	CMB	-0.047	0.187	0.954	0.661 ~ 1.378	0.803	0.552	0.244	1.737	1.077 ~ 2.801	0.024	0.479	0.249	1.615	0.991 ~ 2.631	0.054
RBD	Constant	0.273	0.075	1.313		< 0.001	-1.054	0.626	0.348		0.092	-1.072	0.627	0.342		0.087
	CMB	-0.029	0.161	0.971	0.708 ~ 1.333	0.858	0.148	0.199	1.160	0.786 ~ 1.713	0.455	0.177	0.203	1.193	0.802 ~ 1.776	0.384

Data for core clinical features was shown with "OR (95% CIs)" by binary logistic regressions. All analysis were performed by Crude model, Model 1 (with correction for age at last visit, sex, history of hypertension, T2DM, heart disease, stroke, and the habits of smoking and/or alcohol consumption), and Model 2 (with correction for Model 1 + scores of MTA-max and Fazekas). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

CMBs, cerebral microbleeds; ORs, odd ratios; 95% CIs, 95% confidential intervals; RBD, rapid eye movement sleep behavior disorder

different according to *APOE* ε4 status in all patients with cognitive impairment with Lewy body disease, but no significant differences were found among the four diagnostic subgroups. Several studies have confirmed that CMBs are associated with Aβ deposition regulated by *APOE* genotype in AD [51], while cognitive impairment with Lewy body disease, a disease spectrum dominated by α-syn deposition and accompanied by Aβ or tau deposition, may be less affected by *APOE* ε4 allele. Another possible explanation to the discrepancies could be the variability due to the small sample size in each subgroup. Previous studies have found the burden of Aβ is greater in patients with DLB than in PDD [52], and the higher proportion of CMBs is closely related to increased Aβ load [3, 12]. However, in our data of 22 patients who completed Aβ-PET, we did not find a significant difference in the prevalence of CMBs between the Aβ-negative and Aβ-positive groups, which is consistent with the findings in studies based on neuroimaging and neuropathological studies [13, 45, 53].

Beyond its relationship with stroke, accumulating evidence supports the causal role of CMBs in cognitive decline, motor dysfunction and BPSD in dementia cases. We found that CMBs in cognitive impairment with Lewy body disease were associated with the presence of visual hallucination and fluctuating cognition, but not parkinsonism or RBD, which is controversy with previous studies. Although previous evidence has suggested that cerebral small vessel disease (CSVD) is involved in the pathogenesis of parkinsonism and RBD [11, 18, 32], there is a lack of research on the relationship between CMBs and visual hallucination and fluctuating cognition, and only one study [13] reported no statistically significant association of CMBs with the four core clinical symptoms of DLB. Given the paucity of research, the role of CSVD in the core clinical symptoms of cognitive impairment with Lewy body disease is not clear and needs to be further explored. We also found a result that is consistent with previous studies [54, 55], that is the presence of CMBs increased the symptoms of hallucination, depression, and night-time behavior disturbances, and was associated with the severity of BPSD in all patients, particular in patients with PD-MCI or DLB.

In addition, we found a close association between the presence of CMBs and motor dysfunction in patients with DLB. CMBs can significantly increase the risk of parkinsonism and is positively related to its severity reflected by UPDRS-III and Hoehn-Yahn stage, which are consistent with those of previous studies on the association between CSVD and motor function in Lewy body disease [17, 56]. Several mechanisms may underlie the potential mechanism, including the disruption of dopaminergic pathways and common brain networks [57, 58], dysfunction of the processes of neurodegeneration,

Table 4 Associations between the presence of CMBs and motor function, cognitive performance and BPSD in all cases

		Crude model					Model 1					Model 2				
		Unstandardized Coefficients		*P*	Collinearity Statistics		Unstandardized Coefficients		*P*	Collinearity Statistics		Unstandardized Coefficients		*P*	Collinearity Statistics	
		B	SE		Tolerance	VIF	B	SE		Tolerance	VIF	B	SE		Tolerance	VIF
Motor function																
UPDRS-III	Constant	14.192	0.727	< 0.001			46.130	5.750	< 0.001			46.348	5.648	< 0.001		
	CMB	-0.004	1.569	0.998	1.000	1.000	3.321	1.831	0.070	0.685	1.459	1.415	1.828	0.439	0.652	1.534
Hoehn-Yahn stage	Constant	1.279	0.055	< 0.001			3.647	0.434	< 0.001			3.598	0.429	< 0.001		
	CMB	-0.002	0.119	0.987	1.000	1.000	0.291	0.138	0.035	0.685	1.459	0.190	0.139	0.172	0.652	1.534
Cognitive function																
MMSE	Constant	18.259	0.254	< 0.001			31.678	2.027	< 0.001			30.143	1.816	< 0.001		
	CMB	-1.168	0.549	0.034	1.000	1.000	-1.188	0.643	0.065	0.682	1.465	-0.175	0.586	0.765	0.657	1.522
MoCA	Constant	13.246	0.241	< 0.001			26.799	1.919	< 0.001			25.125	1.664	< 0.001		
	CMB	-1.256	0.522	0.016	1.000	1.000	-1.418	0.608	0.020	0.682	1.465	-0.264	0.537	0.622	0.657	1.522
ADL	Constant	30.056	0.468	< 0.001			6.048	3.742	0.106			8.330	3.527	0.018		
	CMB	2.116	1.013	0.037	1.000	1.000	2.130	1.186	0.073	0.682	1.465	0.494	1.137	0.664	0.657	1.522
CDR	Constant	1.534	0.031	< 0.001			0.105	0.248	0.673			0.316	0.216	0.144		
	CMB	0.141	0.067	0.036	1.000	1.000	0.165	0.079	0.036	0.682	1.465	0.020	0.07	0.769	0.657	1.522
BPSD																
Total-NPI scores	Constant	12.190	0.695	< 0.001			4.566	6.023	0.449			2.840	5.909	0.631		
	CMB	3.250	1.422	0.023	1.000	1.000	3.299	1.796	0.067	0.624	1.602	2.186	1.792	0.223	0.601	1.664
Delusions	Constant	1.202	0.130	< 0.001			-3.539	1.111	0.002			-3.720	1.108	0.001		
	CMB	0.450	0.267	0.093	1.000	1.000	0.289	0.331	0.384	0.624	1.602	0.181	0.336	0.590	0.601	1.664
Hallucinations	Constant	1.856	0.141	< 0.001			-0.708	1.218	0.561			-0.920	1.213	0.449		
	CMB	0.539	0.288	0.062	1.000	1.000	0.858	0.363	0.019	0.624	1.602	0.775	0.368	0.036	0.601	1.664
Agitation	Constant	0.617	0.083	< 0.001			-0.23	0.729	0.752			-0.341	0.722	0.636		
	CMB	0.255	0.171	0.136	1.000	1.000	0.178	0.217	0.414	0.624	1.602	0.027	0.219	0.901	0.601	1.664
Depression	Constant	1.164	0.121	< 0.001			1.981	1.041	0.058			1.812	1.033	0.080		
	CMB	0.294	0.248	0.235	1.000	1.000	0.447	0.31	0.151	0.624	1.602	0.253	0.313	0.420	0.601	1.664
Anxiety	Constant	0.974	0.106	< 0.001			1.802	0.918	0.050			1.673	0.916	0.068		
	CMB	0.209	0.217	0.336	1.000	1.000	-0.061	0.274	0.824	0.624	1.602	-0.162	0.278	0.561	0.601	1.664
Euphoria	Constant	0.101	0.036	0.005			0.215	0.31	0.488			0.195	0.310	0.529		
	CMB	0.128	0.073	0.078	1.000	1.000	0.131	0.092	0.158	0.624	1.602	0.153	0.094	0.104	0.601	1.664
Apathy	Constant	1.395	0.133	< 0.001			2.872	1.157	0.013			2.627	1.146	0.022		
	CMB	-0.110	0.273	0.686	1.000	1.000	-0.062	0.345	0.858	0.624	1.602	-0.245	0.348	0.480	0.601	1.664
Disinhibition	Constant	0.159	0.056	0.005			-0.269	0.485	0.580			-0.296	0.486	0.544		
	CMB	0.475	0.114	< 0.001	1.000	1.000	0.380	0.145	0.009	0.624	1.602	0.363	0.148	0.014	0.601	1.664
Irritability	Constant	0.844	0.098	< 0.001			-1.258	0.851	0.14			-1.412	0.847	0.096		
	CMB	0.468	0.201	0.020	1.000	1.000	0.183	0.254	0.472	0.624	1.602	0.095	0.257	0.712	0.601	1.664

Table 4 (continued)

		Crude model				Model 1				Model 2			
		Unstandardized Coefficients		*P*	Collinearity Statistics	Unstandardized Coefficients		*P*	Collinearity Statistics	Unstandardized Coefficients		*P*	Collinearity Statistics
		B	SE		Tolerance	VIF	B	SE		Tolerance	VIF	B	SE		Tolerance	VIF
Aberrant motor behavior	Constant	1.040	0.128	< 0.001			-1.826	1.101	0.098			-2.011	1.097	0.067		
	CMB	0.327	0.262	0.213	1.000	1.000	0.443	0.328	0.178	0.624	1.602	0.357	0.333	0.284	0.601	1.664
Night-time behavior disturbances	Constant	2.084	0.143	< 0.001			3.194	1.244	0.011			3.012	1.242	0.016		
	CMB	0.228	0.293	0.437	1.000	1.000	0.455	0.371	0.221	0.624	1.602	0.383	0.377	0.310	0.601	1.664
Appetite and eating abnormalities	Constant	0.784	0.092	< 0.001			2.153	0.800	0.007			2.050	0.800	0.011		
	CMB	-0.041	0.188	0.829	1.000	1.000	0.052	0.239	0.828	0.624	1.602	0.007	0.243	0.977	0.601	1.664

Data for motor function, cognitive performance and BPSD was shown with "B ± standard error" by linear regressions, and the VIF diagnosis were also shown. All analysis were performed by Crude model, Model 1 (with correction for age at last visit, sex, history of hypertension, T2DM, heart disease, stroke, and the habits of smoking and/or alcohol consumption), and Model 2 (with correction for Model 1 + scores of MTA-max and Fazekas). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

CMBs, cerebral microbleeds; BPSD, Behavioral and psychological symptoms; UPDRS-III, Unified Parkinson's Disease Rating Scale-Part III; MMSE, the Mini-Mental State Examination; MoCA, the Montreal Cognitive Assessment; ADL, the Activity of Daily Living Scale; CDR, the clinical dementia rating; NPI, the Neuropsychiatric Inventory

neuronal death or dysfunction, and deposition of pathologic proteins [59–61]. We previously showed the higher WMHs burden measured by Fazekas score was associated with the occurrence and severity of parkinsonism in Lewy body dementia [32]. Similarly, cortical and deep white matter degeneration, lacunar infarction, and cerebral amyloid angiopathy can cause or aggravate parkinsonism in patients with or without dementia and may result in a poor prognosis [11, 18, 45]. However, there are few studies on CMBs and motor symptoms in patients with DLB. They also found that the cerebral blood flow was lower in the bilateral basal ganglia and midbrain [62], which were the major region responsibility for motor function, among patients with CMB-positive DLB compared to those with CMB-negative DLB, while it was not clear whether the CMBs in the bilateral basal ganglia and midbrain were related to the hypoperfusion in these regions or to the motor dysfunction. Fukui et al. [8] established the first study to assess clinical and imaging correlations of CMBs in DLB, and clearly proposed that an increased number of CMB was associated with cognitive rather than motor impairment at onset of the disease.

Ample evidence suggests that CSVD, including WMHs, lacunes, and microbleeds, contributes to cognitive function, the course of dementia, and prognosis in normal elderly and patients with AD [43, 46, 49]. Considering the frequent co-occurrence of AD and LBD pathologies and possible interaction between the two diseases, several studies revealed that CSVD also had exert detrimental effect to cognition in PD and DLB [17, 19]. Chen et al. [17]. indicated that a higher CSVD burden was significantly associated with impaired cognition as measured using MMSE and MoCA in patients with PD. Also, in our previous study [32] we found there was a significantly negative associations between Fazekas scores and MoCA in patients with Lewy body dementia. While we did not find any association between CMBs and cognitive function after adjusting for all confounding factors in this study, suggesting that the presence of CMBs may not associated with global cognitive performance of patients with cognitive impairment with Lewy body disease independently of other vascular risk factors. The same finding was found in Mendes et al.'s [13] research, which showed CMBs were not associated with global cognitive performance, executive functioning or speed of information processing in DLB. This maybe because the effect of CMBs combined with Aβ on cognitive function was not sufficient to achieve a significant difference in DLB and PDD, which were characterized with α-syn rather than Aβ.

The major strength of this study is the large-sample size individuals from multicenter, while it also brings some limitations. The burden of CMBs rather than just their presence or absence, their number and distribution are

crucial, data selection bias caused by multi-center study led to the limitation of the effective data we collected and the inability to analyze more variables. In this study, we only analyzed the presence or absence, and general risk factors of CMBs; did not record the potential influence of medications and disease duration on CMBs, not evaluate the diagnostic and differential diagnostic value of CMBs in neurodegenerative diseases. A more robust neuropsychological battery was not available. We just evaluated the association between CMBs and global cognition reflected by MMSE and MoCA, a finding that may be biased between PD-MCI and MCI-LB. We need robust neuropsychological batteries for Lewy body disease to feedback the function of cognitive subdomains. Previous studies have found that the distribution of CMBs and the its synergistic interaction with Aβ, tau and α-syn are related to the occurrence and clinical symptoms of neurodegenerative diseases. However, in this study, only a small sample of Aβ and tau assessment was available, and we did not report the location of CMB, thus affecting further analysis. Moreover, there are also racial differences in the prevalence and distribution of CMBs. The prevalence of CMBs and its distribution in subcortical, deep, and infratentorial structures were higher in Black population than Asian and White population [48, 63]. Our study was only conducted in Chinese population, which limits the generalizability of the findings. It is also important to note that imaging findings while lifetime do not fully represent postmortem pathological findings, since there is a time gap between them. When radiological findings are compared to those in pathological research, the time gap should be considered. Current systematic reviews [64] found that CMBs were common in DLB and PDD, but the prevalence rates were highly variable. The pooled prevalence of CMB was 36% in DLB and 30% in PDD from fourteen studies [64]. Also, the lobar cerebral microbleeds were observed more frequently in DLB than in the PDD [7, 10, 12, 45, 64], whereas the frequencies of deep and infratentorial cerebral microbleeds were not different. CMBs were commonly located in the occipital lobe of patients with DLB, with the frontal cortex being the next most commonly affected followed by the parietal and lastly the temporal cortex [62, 65]. However, these studies lacked data from China. In view of the fact that postmortem pathological examination is difficult to obtain in China, we will continue to collect data to summarize the distribution and characteristics of CSVD based on neuroimaging, and further explore their relationship with AD/PD pathology, motor and non-motor symptoms of cognitive impairment with Lewy body disease.

Conclusions

DLB had a higher proportion of CMBs than PDD, MCI-LB and PD-MCI. The presence of CMBs may contribute to core clinical symptoms, motor dysfunction and BPSD in patients with cognitive impairment with Lewy body disease. Prevention and management of CMBs through strict control of modifiable cerebrovascular risk factors, such as hypertension and diabetes, may be a clinically meaningful intervention to maintain motor and non-motor functions in cognitive impairment with Lewy body disease.

Abbreviations

α-Syn	Alpha-synuclein
AD	Alzheimer's disease
Aβ	Amyloidβ
ADL	Activities of daily living
APOE	Apolipoprotein E
BPSD	Behavioral and psychological symptoms in dementia
CDR	Clinical dementia rating
CMBs	Cerebral microbleeds
CSVD	Cerebral small vessel disease
DLB	Dementia with Lewy bodies
GRE	Gradient recalled echo
MCI	Mild cognitive impairment
MCI-LB	Mild cognitive impairment with Lewy bodies
MMSE	Mini-mental state examination
MoCA	Montreal cognitive assessment
MTA	Medial temporal lobe atrophy
PD	Parkinson's disease
PDD	Parkinson disease dementia
PD-MCI	Parkinson's disease with MCI
NPI	Neuropsychiatric Inventory
RBD	Rapid eye movement sleep behavior disorder
SWI	Susceptibility weighted imaging
T2DM	Type-2 diabetes
UPDRS-III	Unified parkinson's disease rating scale-part III
WMH	White matter hyperintensity

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-025-04181-w.

Supplementary Material 1: **Supplementary Fig. 1** Schematic representations of CMBs on part of scanners. **Supplementary Table 1** Demographic and clinical characteristics of MCI-LB, PD-MCI, DLB and PDD. **Supplementary Table 2** The proportions of CMBs in patients sub-grouped by APOE ε4 allele, Aβ and tau. **Supplementary Table 3** Associations between the presence of CMBs and BPSD in all cases. **Supplementary Table 4** Associations between CMBs and clinical features in DLB cases. **Supplementary Table 5** Associations between CMBs and clinical features in MCI-LB cases. **Supplementary Table 6** Associations between CMBs and clinical features in PD-MCI cases. **Supplementary Table 7** Associations between CMBs and clinical features in PDD cases.

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Author contributions

Dr. Yong Ji had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design were performed by Yong Ji. All authors, including Guili Zhang and Zhihong Shi, contribute to collect medical records, and the acquisition, analysis, or interpretation of data. Jinghuan Gan wrote the first draft of the manuscript, Zhihong Ren, Jinghuan Gan and Shuai Liu contributed to the critical revision of the manuscript for important intellectual content. Statistical analysis was performed by Zhichao Chen and Hao Lu. Fundings were obtained from Yong Ji. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The Ethics Committees of the 22 centers approved all research activities in this multicenter study and waived informed consent because the data were pseudonymized from registers. The procedures were performed in accordance with the ethical standards of the Committee on Human Experimentation.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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