Cerebral small vessel disease is associated with concurrent physical and cognitive impairments at preclinical stage

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1. Introduction

Physical and cognitive performance are the major domains of functional ability that affect healthy aging [1,2]. Evidence indicates that physical frailty and cognitive impairment interact significantly during the aging process [3,4]. Several studies have found that physical frailty, particularly gait slowness and handgrip weakness, may increase the risk of future cognitive declines and predict incident dementia of all types [5,6]. In a recent meta-analysis, the risk for dementia was higher among older people with concurrent physical frailty and cognitive impairment compared to those with only cognitive impairment [7]. Therefore, geriatricians have suggested a clinical phenotype of concurrent physical frailty and cognitive impairment, which could predict future dementia, disability and mortality and help identify the target population with risks of accelerated aging in the community-dwelling elderly. And hopefully, by studying its pathophysiology, we could develop an effective management strategy to reverse the trajectories toward unhealthy aging.

Several operational definitions of this phenotype have been proposed including cognitive frailty, motoric cognitive risk syndrome and physiocognitive syndrome (PCDS) [8]. PCDS is defined as concurrent mobility impairment (slow gait or/and weak handgrip but without disable) and...
cognitive impairment (≥1.5 SD below the mean for age-, sex-, and education-matched norms in any cognitive domain but without dementia). In Asian countries, PCDS has a good performance; this defined criterion could identify around 10–15% of community-dwelling older persons without dementia or disability, who are at increased risk for incident disability (Hazard ratio [HR] 3.9, 95% confidence interval [95% CI] 3.0–5.1), incident dementia (HR 3.4, 95% CI 2.4–5.0) and all-cause mortality (HR 6.7, 95% CI 1.8–26.1) [9–13]. The concept and operational definition of PCDS were established by consensus and formally proposed at the 5th Asian Conference of Frailty and Sarcopenia in 2019 [14].

Aging process or vascular risk factors cause pathologies in brain microvessels such as arteriosclerosis, lipohyalinosis and amyloid angiopathy [15]. These age-related microvascular pathologies might result in brain parenchymal lesions including brain white matter changes, small infarcts or microhemorrhages which could be detected by brain magnetic resonance imaging (MRI) [15,16]. Brain small vessel disease (SVD) is now diagnosed by these common MRI markers, e.g. severe white matter hyperintensity (WMH), lacune and cerebral microbleed (CMB) [16,17]. SVD is an important etiology of dementia and stroke in the elderly [15]. In several community-based brain MRI cohort studies, before stroke or dementia events occurring, the presence and severity of SVD were also significantly associated with worse cognitive function in the elderly [15–18]. Therefore, we wondered whether asymptomatic (non-demented non-stroke) SVD plays a role in PCDS, a phenotype of accelerated functional decline or accelerated aging. The present study cross-sectionally analyzed the high resolution 3T brain MRI images of a community-based population aged ≥ 50 years and aimed to evaluate the associations between SVD and PCDS.

2. Methods

2.1. Study population

The I-Lan Longitudinal Aging Study (ILAS) is a community-based aging cohort study in I-Lan County, Taiwan, that aims to evaluate the mechanisms of unhealthy aging at an early, preclinical stage [19]. Community-dwelling adults aged ≥50 years from Yuanshan Township in I-Lan County were invited to participate. The initial wave of participants was recruited between August 2011 and July 2014. The inclusion criteria of the ILAS were as follows: (1) inhabitants of I-Lan County who were not planning to move soon and (2) aged ≥50 years. In addition, participants who met any of the following conditions were excluded: (1) inability to communicate and complete an interview; (2) inability to complete a simple motor task (for example, a 6-m walk) due to functional disability, (3) presence of any major illness with associated decreased life expectancy (less than 6 months), (4) presence of any institutionalization for any reason. In addition, participants diagnosed with neuropsychiatric diseases, such as dementia, stroke, brain tumor, or major depression, were excluded from the present study.

A questionnaire that included information on demographics, educational years, smoking habits, and medical history was assessed. The presence of vascular risk factors such as hypertension, diabetes mellitus, dyslipidemia, and smoking habit were determined by history taking or laboratory investigation. Hypertension was defined as a self-report of a current antihypertensive medication prescription, or as a measurement of systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. Diabetes mellitus was defined as self-report of current diabetes treatment, or a measurement of HgbA1c ≥ 6.5%. Dyslipidemia was recorded if there was a self-report of the use of statins, or a blood level of total cholesterol ≥ 240 mg/dL.

2.2. Standard protocol approval, registration, and patient consent

The study was approved by the Institutional Review Board of the National Yang-Ming University, Taipei, Taiwan (IRB no. YM109161F). All participants provided written informed consent. All methods were carried out in accordance with relevant guidelines and regulations.

2.3. Physical assessment

Handgrip strength of the dominant hand was measured using digital dynamometry (Smedley’s Dynamo Meter; TTM, Tokyo, Japan); participants sat with their arms by their sides and the best of three readings was used for analysis. The 6-m usual walking speed during dynamic walking and without deceleration was used to assess the gait speed and to define slowness.

2.4. Cognitive assessment

All participants received a face-to-face neuropsychological assessment administered by trained interviewers at baseline and follow-up, including the Mini-Mental State Examination (MMSE) and neuropsychological tests of different cognitive domains:

- Verbal memory: delayed recall in the Chinese Version Verbal Learning Test
- Language: Boston Naming Test, and category (animal) Verbal Fluency Test
- Visuospatial function: Taylor Complex Figure Test
- Executive function: Backward Digit and Clock Drawing Test

2.5. Definitions of PCDS

Mobility impairment was defined as gait slowness and/or handgrip weakness (by cut-offs from the 2019 consensus update of the Asian Working Group for Sarcopenia) [20]. Cognitive impairment was defined as cognitive performance ≥1.5 SD below the mean for age-, sex-, and education-matched controls in any of cognitive domains assessed by our comprehensive objective neuropsychological tests. PCDS was defined as concurrent mobility and cognitive impairments [8]. Participants with isolated mobility impairment would be classified as mobility impairment without disable (MIND) while participants with isolated cognitive impairment would be classified as cognitive impairment without dementia (CIND). Thus, study population would be stratified into four groups, e.g. robust, CIND, MIND and PCDS groups.

2.6. Brain MRI acquisitions

Multimodal neuroimaging acquisition was performed at the National Yang-Ming University to obtain GSVD markers for each participant, including WMH, lacunes, and CMBs. All MRI scans were collected on a single 3Tesla Siemens MRI scanner (Siemens Magnetom Tim Trio, Erlangen, Germany) with a vendor-supplied 12-channel phased-array head coil. All acquired whole-brain MRI scans were without inter-slice gap and interolation. The following imaging sequences were used. First, T1-weighted images were acquired using a three-dimensional T1-weighted magnetisation-prepared rapid-acquisition gradient echo sequence (repetition time [TR]/echo time [TE]/inversion time [TI] = 3500/3.5/1100 ms; flip angle = 7°; number of excitations [NEX] = 1); field of view (FOV) = 256 × 256 mm; matrix size = 256 × 256; 192 sagittal slices; and voxel size = 1.0 mm³). Second, T2-weighted fluid-attenuated inversion recovery (FLAIR) images were acquired using a two-dimensional T2-weighted FLAIR multishot turbo-spin-echo sequence (TR/TE/TI = 9000/143/2500 ms; flip angle = 130°; NEX = 1; FOV = 220 × 220 mm; matrix size= 320 × 320, echo train length = 35; 63 axial slices; and voxel size = 0.69 mm × 0.69 mm × 2.0 mm). Third, susceptibility-weighted images (SWI) were acquired using a three-dimensional SWI sequence (TR/TE = 28/21 ms; flip angle = 15°, FOV = 256 × 224 mm; matrix size = 256 × 224; 88 axial slices; bandwidth = 120 Hz/Px; and voxel size = 1.0 × 1.0 × 2.0 mm). Before the
image pre-processing, all the acquired MRI scans were visually examined by an experienced neuroradiologist to exclude any data with severe motion artifacts or gross brain abnormalities including trauma, tumor, and intracerebral hemorrhagic or territorial infarct lesions (in the territory of large arteries or their branches but not of a perforating artery).

2.7. Volume quantification of WMH

We applied the previously established analytical framework to estimate volumetric information of multiple tissue types for each individual [18]. All the following analyses were conducted with Statistical Parametric Mapping (SPM12, version 7487, Wellcome Institute of Neurology, University College London, UK, http://www.fil.ion.ucl.ac.uk/spm/) and Matlab R2016a (The Mathworks, Inc., Natick, MA, USA) using default settings. First, individual T2-weighted FLAIR scan was affine-registered to the corresponding T1-weighted scan, and then served as the inputs for generating a native T1 space WMH probability map and lesion-filled T1 images using the Lesion Segmentation Toolbox (LST, version 3.0.0, https://www.applied-statistics.de/lst.html) (Fig. 1). Second, all the lesion-filled T1 anatomical scans were processed using the standard Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra–voxel based morphometry (DARTEL-VBM) approach to obtain the corresponding deformation field for each individual. Finally, all the native T1 space tissue probability maps (including grey matter, white matter, cerebrospinal fluid and WMH) were spatial transformed into the standard Montreal neurological institute (MNI) space using subject-specific deformation field and then modulated to obtain absolute volumetric information of total intracranial volume (TIV, summation of grey matter volume, white matter volume and cerebrospinal fluid volume) and WMH volume simultaneously.

2.8. Detection and assessment of other SVD MRI markers [17]

Lacunes were assessed using T2-weighted FLAIR anatomical scans. Lacunes are defined as small (<15 mm in diameter) cerebrospinal fluid-containing cavities, located in the deep gray or white matter, with adjacent WMH. CMBs were defined as small, rounded or circular, well-defined, hypointense lesions within the brain parenchyma with clear margins and ≤10 mm in size on SWI. Microbleed mimics, such as vessels, calcification, partial volume, air-bone interfaces, and hemorrhages

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Fig. 1. Example of white matter hyperintensity segmentation.
within or adjacent to an infarct, were carefully excluded. Intra-rater reliability was assessed by evaluating CMBs in 20 randomly sampled images at a separate time (k, 0.83; 95% confidence interval [CI], 0.79–0.90). We also reassessed CMBs in the 25 randomly sampled images previously assessed by Dr. Chung and another investigator (k, 0.82; 95% CI, 0.79–0.88). CMBs were classified into deep, infratentorial, and lobar categories. Individuals with CMBs were divided into two types according to the CMB topography: strictly lobar (CMB exclusively located in lobar regions) and mixed CMB (deep and/or infratentorial CMB with or without lobar CMB).

2.9. Definition of SVD

We used a simple SVD score to represent the SVD burden [21]. One point was given for the presence of any lacune, severe WMH (defined as >50th percentile of WMH volume/TIV ratio [0.07%]), and CMB; thus, the simple SVD score ranged from 0 to 3. We defined participants of SVD as having SVD score ≥ 2.

3. Statistical analyses

Analyses were performed using SPSS version 22.0. (IBM, Armonk, NY, USA). All data are presented as mean (standard deviation, SD) or median (range) for continuous variables and number (percentage) for discrete variables. Group comparisons were made using the nonparametric Kruskal-Wallis test with post-hoc analyses. When appropriate, chi-square or Fisher’s exact tests were performed for categorical variables. Multivariate regression analyses were performed to evaluate the independent associations between SVD and PCDS. The covariates included the age, sex, vascular risk factors (presence of hypertension, diabetes mellitus, and dyslipidemia and cigarette smoking habits) or/and each SVD marker. Odds-ratios (ORs) with 95% CIs would be provided. P value < 0.05 was considered statistically significant. SVD population attributable risk fraction of PCDS was measured as (observed case number of PCDS with SVD exposure minus estimated (expected) case number of PCDS with no SVD exposure)/case number of SVD.

4. Results

Among the initial sampling population of the ILAS recruited between August 2011 and July 2014, 760 individuals without stroke and dementia had received comprehensive MRI modalities for SVD detection and evaluation. We excluded nine individuals with incidentally found brain tumors, 16 individuals with problematic images due to head motion and 26 individuals without sufficient physical and cognitive assessments. There were 709 participants’ data and neuroimaging eventually included in the analyses. A flow chart of the study population is illustrated in Fig. 2. There were 317 (44.7%) classified as robust group, 212 (29.9%) as CIND group, 117 (16.5%) as MIND group and 63 (8.9%) as PCDS group.

Demographic and clinical data of the study population are demonstrated in Table 1. PCDS and MIND groups had the oldest ages; these two groups, respectively, were older than the robust and the CIND groups revealed by post-hoc analyses. Four groups had similar sex distributions. As to the frequency of vascular risk factors, PCDS had more prevalent hypertension, diabetes mellitus and dyslipidemia with statistical significance in the frequency of diabetes mellitus. There was also significant difference in the frequency of cigarette smoking habits between groups; MIND had the most prevalent cigarette smoking habits. Post-hoc analyses showed that PCDS and MIND, respectively, had slower gait and weaker handgrip strength than CIND and the robust. In group comparisons of cognitive functional tests with post-hoc analyses, PCDS had lower scores than MIND and than robust in all cognitive domains. The results also showed that PCDS had lower scores than the CIND in all cognitive tests except in clock drawing test.

4.1. SVD profiles in four groups

Table 2 shows the details and comparisons of SVD profiles among four groups. The results showed a significant difference of SVD severity (SVD score) among four groups. PCDS group had the least proportion of people with SVD score zero (28.2% versus 42.9–52.4% in the other three groups) and the most proportion of people with severe SVD (SVD score ≥ 2; 33.3% versus 11.3–19.1% in the other three groups) (Table 2; Fig. 3A). We also tested whether there were group differences in the profiles of each SVD marker (Table 2; Fig. 3B-E). The results showed significant differences in the frequencies of severe WMH (> 50th percentile of WMHV/TIV ratio) and lacune(s) among groups. As to the CMB profiles, the results depended on their topographic characteristics; group differences only showed significance in the frequencies of mixed...
and PCDS factors (Table 3). The results showed that SVD (SVD score ≥ 2) was significantly associated with PCDS, concurrent mobility physical and cognitive impairments (MIND) or isolated cognitive impairment (CIND). People of SVD had an OR of 2.3 developing PCDS compared with people of non-SVD, which was independent of age, sex and vascular risk factors.

4.2. Multivariate analyses of associations between SVD (SVD score ≥ 2) and PCDS

To validate the independent association between SVD and PCDS, we performed multivariate analyses adjusting for age, sex and vascular risk factors (Table 3). The results showed that SVD (SVD score ≥ 2) was significantly associated with PCDS, concurrent mobility physical and cognitive impairments (MIND) or isolated cognitive impairment (CIND). People of SVD had an OR of 2.3 developing PCDS compared with people of non-SVD, which was independent of age, sex and vascular risk factors.

5. Discussion

The main finding is that, at an early, preclinical stage, SVD (SVD score ≥ 2) was significantly associated with PCDS, a phenotype of concurrent physical and cognitive impairment, but not isolated physical or cognitive impairment. In addition, among three common SVD markers (WMH, lacune and CMB), the presence of lacune and severe WMH, respectively, were significantly correlated with PCDS. These significant associations were independent of age, sex and vascular risk factors. SVD is the primary cause of vascular cognitive impairment/dementia.
Fig. 3. Frequency of cerebral small vessel disease (SVD score ≥ 2) and each SVD marker in four groups and group comparisons with chi-square tests.

SVD attributable risk fraction of PCDS = 21.1%

Fig. 4. The proportion of PCDS attributable to SVD.
Model 1: adjusted for age and sex; model 2: adjusted for age, sex and vascular risk factors (hypertension, diabetes mellitus, dyslipidemia and cigarette smoking).

Abbreviations: CIND = cognitive impairment no dementia; MIND = mobility impairment no disable; PCDS = physio-cognitive decline syndrome; SVD = cerebral small vessel disease; OR = odds ratio; 95% CI = 95% confidence interval.

Table 3
Multivariate analyses of associations between cerebral small vessel disease (SVD score ≥ 2) and physio-cognitive decline syndrome.

| SVD versus non-SVD | Model 1 | Model 2 |
|--------------------|---------|---------|
|                    | 95% CI  | p value | 95% CI  | p value |
| Robust             | Ref.    | –       | Ref.    | –       |
| CIND               | 0.8     | 0.5-1.5 | 0.543   | 0.8     | 0.5-1.5 | 0.515 |
| MIND               | 1.2     | 0.6-2.5 | 0.666   | 1.2     | 0.6-2.6 | 0.640 |
| PCDS               | 2.5     | 1.4-4.3 | 0.001   | 2.3     | 1.3-4.0 | 0.003 |

Model 1: adjusted for age and sex; model 2: adjusted for age, sex and vascular risk factors (hypertension, diabetes mellitus, dyslipidemia and cigarette smoking).

Abbreviations: CIND = cognitive impairment no dementia; MIND = mobility impairment no disable; PCDS = physio-cognitive decline syndrome; SVD = cerebral small vessel disease; OR = odds ratio; 95% CI = 95% confidence interval.

Table 4
Multivariate analyses of associations between each cerebral small vessel disease marker and physio-cognitive decline syndrome.

| Severe WMHV/TIV ratio | Model 1 | Model 2 |
|-----------------------|---------|---------|
|                      | OR 95% CI | p value | OR 95% CI | p value |
| Robust               | Ref. –   | –       | Ref. –   | –       |
| CIND                 | 1.4     | 1.0-2.1 | 0.121   | 1.4     | 0.9-2.2 | 0.113 |
| MIND                 | 1.1     | 0.5-2.9 | 0.9     | 0.5-2.5 | 0.812 |
| PCDS                 | 1.9     | 1.0-3.8 | 0.023   | 1.6     | 0.9-2.8 | 0.086 |
| The presence of lacune | OR 95% CI | p value | OR 95% CI | p value |
| Robust               | Ref. –   | –       | Ref. –   | –       |
| CIND                 | 1.1     | 0.6-2.2 | 0.742   | 1.1     | 0.6-2.2 | 0.753 |
| MIND                 | 1.4     | 0.6-3.0 | 0.501   | 1.3     | 0.5-3.3 | 0.608 |
| PCDS                 | 2.5     | 1.3-4.8 | 0.005   | 2.1     | 1.1-4.1 | 0.036 |
| The presence of mixed CMB | OR 95% CI | p value | OR 95% CI | p value |
| Robust               | Ref. –   | –       | Ref. –   | –       |
| CIND                 | 0.7     | 0.3-1.6 | 0.446   | 0.7     | 0.3-1.6 | 0.297 |
| MIND                 | 1.4     | 0.5-3.5 | 0.489   | 1.3     | 0.5-3.5 | 0.626 |
| PCDS                 | 2.0     | 1.0-4.1 | 0.058   | 1.4     | 0.7-4.1 | 0.349 |
| The presence of strictly lobar CMB | OR 95% CI | p value | OR 95% CI | p value |
| Robust               | Ref. –   | –       | Ref. –   | –       |
| CIND                 | 0.6     | 0.3-1.5 | 0.295   | 0.6     | 0.3-1.5 | 0.269 |
| MIND                 | 0.7     | 0.2-1.5 | 0.575   | 0.7     | 0.2-1.5 | 0.602 |
| PCDS                 | 0.7     | 0.3-1.9 | 0.519   | 0.8     | 0.3-1.9 | 0.638 |

Model 1: adjusted for age, sex and vascular risk factors (hypertension, diabetes mellitus, dyslipidemia and cigarette smoking); model 2: adjusted for age, sex, vascular risk factors and other SVD markers (the presence of severe WMHV/TIV ratio, lacune, mixed CMB and strictly lobar CMB).

Abbreviations: CIND = cognitive impairment no dementia; MIND = mobility impairment no disable; PCDS = physio-cognitive decline syndrome; SVD = cerebral small vessel disease; CMB = cerebral microbleed; OR = odds ratio; 95% CI = 95% confidence interval.

[22] and also associated with Alzheimer’s dementia [23]. However, the nature or characteristics of impaired cognitive profile in SVD has not been determined. A recent systemic-review and meta-analysis shows that SVD is not only affected executive function and processing speed as previously thought, but also other cognitive domains [24]. Therefore, it is recommended the use of comprehensive neuropsychological tests for SVD research and clinical applications. We have used neuropsychological tests covering several cognitive domains to define cognitive impairment in PCDS. Notably, in our population, PCDS group who was identified with concurrent mobility and cognitive impairments had worse cognitive performances than isolated cognitive impairment group (CIND). The present study revealing significant associations between SVD with PCDS but not isolated cognitive or physical impairments have provided insights into the clinical manifestations of asymptomatic SVD; our results indicate that cognitive impairment in early stage of SVD is accompanied with concurrent physical impairment. Therefore, we suggest that, in addition to comprehensive neuropsychological tests of multiple domains, physical evaluations (particularly gait speed and handgrip strength) are also needed to capture the thorough clinical pictures of SVD.

Previous epidemiological studies have found that frailty is a risk factor of both vascular dementia and Alzheimer’s dementia [1–7]. An autopsy study recently published also revealed that frailty was associated with global cognitive function and dementia independent of Alzheimer’s and neurovascular neuropathological burdens [25]. The present study showed that 21.1% of PCDS were attributable to the presence of SVD; this fraction of PCDS population might be prevented when SVD lesions were reversed or mitigated. These results indicate that PCDS might be a multiply determined condition, and thus the evaluation and management strategy for PCDS should be multifactorial.

The operational definition of PCDS efficiently identifies the elderly who are at higher risk of accelerating aging [8–13]. Most importantly, functional declines in people with PCDS are potentially reversible or being slowed down. The Taiwan Health promotion Intervention Study for Community Elders (THISC), a cluster-randomized controlled trial, evaluated a participatory multidomain intervention in community-dwelling ≥65-year-olds, which integrated physical exercise, cognitive training, nutrition advice, and disease management education [26]. A secondary THISC sub-analysis showed that the multidomain intervention significantly improved cognitive dysfunction in older people with PCDS [27]. Elderly with PCDS seem to be at a critical point toward unhealthy aging. In addition to serving as a phenotype to be identified and to intervene for public health use, we have used PCDS as a study target to evaluate the physiopathology of and develop the mechanism-based management strategy [8,28]. The present study showed that neurovascular aging, e.g. SVD, is involved in this specific geriatric manifestation of concurrent physical and cognitive impairments. We also demonstrated the relationship between each SVD marker and PCDS. The results suggest that (1) ischemic SVD (lacune with WMH) instead of bleeding SVD (CMB) and (2) hypertensive vasculopathy (presented with mixed CMB) instead of cerebral amyloid angiopathy (presented with strictly lobar CMB), [18,29] are more relevant to the development of PCDS. Therefore, interventions to prevent SVD such as hypertension control might also reverse or prevent further functional declines in the elderly with PCDS.

There are method issues needed to be concerned. We assessed the severity of WMH using semiautomated volumetric measurement since it offers a more reliable, sensitive, and objective alternative to visual rating scales [30]. The present study defined the presence of severe WMH as > 50th percentile of WMH/total intracranial volume ratio in our study population. The cut-off point of the WMH volume ratio for defining severe WMH might differ between populations. Secondly, since we wanted to elucidate the pathophysiology at the earlier, preclinical stage of unhealthy aging, the present findings were from the community-based community who had no stroke or dementia. Whether the present results of associated clinical features in SVD could be generalized to other population with evident clinical events needs more validation studies. Last, we would need longitudinal studies to validate the causal role of SVD in PCDS.
Declaration of Competing Interest
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References
[1] T Hedden, JD. Gabrieli, Insights into the ageing mind: a view from cognitive neuroscience, Nat. Rev. Neurosci. 5 (2004) 87–96, https://doi.org/10.1038/nrn1322.
[2] JE. Morley, The new geriatric giants, Clin. Geriatr. Med. 33 (2017) xi–xii, https://doi.org/10.1016/j.cger.2017.05.001.
[3] F Panza, M Lozupone, D Seripa, A Pilotto, G. Logroscino, Cognitive frailty: a systematic review of epidemiological and neurobiological evidence of an age-related clinical condition, Rejuvenation Res. 18 (2015) 389–412, https://doi.org/10.1007/s12696-014-9346-7.
[4] G. Logroscino, A subtlety of definition: frailty in different clinical settings, J. Nutr. Health Aging 25 (10) (2021) 1179–1189, https://doi.org/10.1007/s12603-021-1693-4.
[5] CP Chung, WJ Lee, LN Peng, H Shimada, TF Tsai, CP Lin, H Arai, CK Liang, WJ Lee, CH Loh, ILAS Research Group, Comparisons of a visual rating scale with a volumetric measurement, AJNR Am. J. Neuroradiol. 27 (2006) 875–882, https://doi.org/10.1093/ajnr/ajn206.
[6] WJ Lee, CP Chung, Y Ito, S Lee, H Park, T Suzuki, Combined prevalence of frailty and mild cognitive impairment in a population of elderly Japanese people, J. Am. Med. Dir. Assoc. 14 (2013) 518–524, https://doi.org/10.1016/j.jamda.2013.03.010.
[7] H Shimada, CK Liang, WJ Lee, H Arai, Cognitive frailty predicts incident dementia among community-dwelling older people, J. Clin. Med. 7 (2018) 250, https://doi.org/10.3390/jcm7020250.
[8] H Shimada, M Makizako, T Doi, Y Yoshida, K Yuutsumimoto, Y Anan, K Uemura, T Ito, S Lee, H Park, Combined prevalence of frailty and mild cognitive impairment in a population of elderly Japanese people, J. Am. Med. Dir. Assoc. 14 (2013) 518–524, https://doi.org/10.1016/j.jamda.2013.03.010.
[9] CH Loh, H Arai, Cognitive frailty as a predictor of dementia among older adults: a systematic review and meta-analysis, Alzheimer's Dement 17 (2021) 665–685, https://doi.org/10.1016/j.jalz.2020.10.002.
[10] LM Wallace, O Theou, S Darvesh, DA Bennett, AS Buchman, MA Andrew, SA Kirkland, JD Fisk, K Rockwood, Neuropsychological burden and the degree of frailty in relation to global cognition and dementia, Neurology 94 (2020) e1294–e1302, https://doi.org/10.1212/WNL.0000000000010944.
[11] LC Chen, AC Hwang, CH Loh, ILAS Research Group, Cerebral small vessel disease: A systematic review and meta-analysis, Alzheimers Dement 17 (2021) 25336, https://doi.org/10.1016/j.jalz.2020.10.002.
[12] WJ Lee, CK Liang, WJ Lee, LN Peng, H Shimada, TF Tsai, CP Lin, H Arai, Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges, Lancet Neurol. 9 (2010) 689–701, https://doi.org/10.1016/S1474-4422(10)70104-6.
[13] JM Wardlaw, EM Smith, TJ F品类, RF Carter, RC. Hellyer, PA. Hawkes, Vascular imaging and clinical application of cerebrovascular disease, Lancet Neurol. 18 (7) (2019 Jul) 684–696, https://doi.org/10.1016/S1474-4422(19)30079-1.
[14] L. Pantoni, Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges, Lancet Neurol. 9 (2010) 689–701, https://doi.org/10.1016/S1474-4422(10)70104-6.
[15] JM Wardlaw, EE Smith, GJ Bocksels, C Cordonnier, F Farrer, FL. Hellyer, J. Searle, RC. Hellyer, WB. Carter, RC. Hellyer, PA. Hawkes, R Thompson, RC. Hellyer, AJ Stevenson, JM. Wardlaw, Cognitive impairment in sporadic cerebral small vessel disease: A systematic review and meta-analysis, Alzheimers Dement 17 (2021) 665–685, https://doi.org/10.1016/j.jalz.2020.10.002.
[16] K Amin Al Olama, JMS Wason, AM Tuladhar, EMC van Leijsen, MA. Koini, E Hofer, OA Skrobot, CB. Black, C Chen, DC. Carlı, ER. Kirkpatrick, J. Stobborough, JM. Wardlaw, Cognitive frailty as a risk factor for incident disability during late life: a 24-month follow-up longitudinal study, J. Nutr. Health Aging 24 (2020) 494–499, https://doi.org/10.1007/s12603-020-1365-5.
[17] LK Chen, H Arai, Physical cognitive decline as the accelerated aging phenotype, Arch. Gerontol. Geriatr. 88 (2020), 104501, https://doi.org/10.1016/j.archger.2020.104501.
[18] CH Loh, H Arai, LK. Chen, Cerebral small vessel disease: mechanisms and clinical implications, Lancet Neurol. 18 (7) (2019 Jul) 684–696, https://doi.org/10.1016/S1474-4422(19)30079-1.
[19] T Ito, S Lee, H Park, T Suzuki, Combined prevalence of frailty and mild cognitive impairment in a population of elderly Japanese people, J. Am. Med. Dir. Assoc. 14 (2013) 518–524, https://doi.org/10.1016/j.jamda.2013.03.010.
[20] H Shimada, M Makizako, T Doi, H Arai, Cognitive frailty predicts incident dementia among community-dwelling older people, J. Clin. Med. 7 (2018) 250, https://doi.org/10.3390/jcm7020250.