Supplementary Methods

Data availability

All data from this article are being held within National Taiwan University Hospital (NTUH) and will be shared with qualified investigators on request.

Participant enrollment

We prospectively recruited patients aged ≥20 years who had suffered symptomatic spontaneous intracerebral hemorrhage (ICH) from September 2014 onward to undergo brain magnetic resonance imaging (MRI) and ^{11}C-Pittsburgh compound B (PiB) positron emission tomography (PET) scans at NTUH.[1,2] A total of 169 survivors of ICH who met the enrollment criteria agreed to participate in this study and underwent brain MRI and PiB PET scans. Median time from ICH to amyloid PET was 6.8 months. Baseline clinical data were collected by the investigators through a comprehensive review of medical records and by interviewing each participant. We gathered information on the following demographic characteristics: age, sex, years of education, diagnoses of chronic hypertension, diabetes, or hypercholesterolemia, and renal function (represented by the estimated glomerular filtration rate). At enrollment, each participant's cognitive status was assessed through a combination of history taking and objective cognitive testing, which included the Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR) scores.

Follow-up data

The cognitive status of each participant was followed up at our neurology clinic during regular visits; cognitive evaluations were routinely performed as part of routine clinical protocols by neuropsychologists, starting at the enrollment date (i.e., the date of the PiB scan). A diagnosis of dementia was based on the National Institute on Aging-Alzheimer's Association criteria for all-cause dementia, which requires that patients exhibit cognitive or behavioral symptoms that interfere with their ability to function at work or in daily activities, represent a decline from previous levels, and are not explained by delirium or a major psychiatric disorder.[3] For the purpose of this study, patients without cognitive complaints who did not undergo a cognitive assessment at the clinic were asked to complete a formal interview with our neuropsychologist to confirm their cognitive status. Cognitive decline was defined as meeting at least one of the following criteria: (1) conversion to dementia, (2) a ≥1-point increase in the CDR score for participants already diagnosed with dementia at baseline, or (3) a ≥2-point decrease in the MMSE score. Of the overall cohort, the 99 participants who underwent at least one follow-up cognitive assessment (except for baseline assessment) were included in the longitudinal analysis.

MRI acquisition and analysis

Brain MRI scans were obtained using either a 1.5 T (Siemens Aera; Siemens Corp., Sacramento, CA, USA) or 3 T (Siemens Verio; Siemens Corp., Sacramento, CA, USA) scanner. The imaging protocols included T1-weighted imaging, T2-weighted imaging, fluid-attenuated inversion recovery (FLAIR) imaging, susceptibility-weighted imaging (SWI), diffusion-weighted imaging, apparent diffusion coefficient maps, and 3D T1-weighted magnetization-prepared rapid acquisition gradient echo imaging at 1-mm slice thickness, as previously described.[1,2] 3D FLAIR imaging at a 1-mm slice thickness was performed for a subset of participants (n=19). According to the Boston criteria 2.0,[4] patients with lobar ICH(s) involving the cerebral cortex and underlying white matter with strictly lobar cerebral microbleeds (CMBs), cortical superficial siderosis (cSS), or specific white matter features (severe perivascular spaces [PVS] in the centrum semiovale or white matter hyperintensities [WMHs] in a multispot pattern) were classified as having probable cerebral amyloid angiopathy.

The presence and number of durable cortical cerebral microinfarcts (CMIs) were evaluated by experienced neurologists or neuroradiologists (P-T. C. and B-C. L.) blinded to the results of amyloid PET and cognitive outcomes, as previously described.[5,6] Briefly, CMIs appear hypointense on T1-weighted images (isointense with CSF), hyperintense or isointense (relative to surrounding tissue) on FLAIR sequences, and hyperintense on T2-weighted images. CMIs must be detectable on at least two views of the brain (e.g., sagittal and transverse), restricted to the cortex, distinct from PVS, and measure ≤4 mm in their greatest dimension. A lesion compatible with a microinfarct on 3D T1-weighted images but not detectable as a hyperintense lesion on 2D T2-weighted images (due to lesion orientation or slice thickness) can still be accepted as a microinfarct if the corresponding T2*-weighted image is not hypointense at the same site.[6]

Other MRI markers related to cerebral small vessel disease (SVD) were evaluated according to the updated Standards for Reporting Vascular Changes on Neuroimaging criteria.[1,7-9] Briefly, the number of CMBs and the presence of cSS were evaluated using axial SWI sequences.[10,11] The number of CMBs in the lobar (i.e., the frontal, temporal, parietal, occipital, and insular cortices) and deep regions (i.e., the brainstem, basal ganglia, thalamus, internal capsule, external capsule, corpus callosum, and deep periventricular white matter) was counted. Lacunes were evaluated in the supratentorial region and defined as "round or ovoid, subcortical, fluid-filled cavities, ranging from 3 to 15 mm in diameter."[12,13] The severity of WMH in both the periventricu-

lar and deep brain regions was rated using the Fazekas scale[14]; the highest score was considered as the overall WMH score for each participant. WMH volume was calculated based on fluid-attenuated inversion recovery imaging of the ICH-free hemisphere and multiplied by two, as we previously proposed.[1] MRI-visible PVS were evaluated on T2-weighted imaging, and defined as sharply delineated structures measuring <3 mm following the course of perforating or medullary vessels.[15] High-degree PVS was defined as >20 visible PVS in the centrum semiovale or in the BG on the side of the brain with more severe involvement.[15,16] The total SVD score (range, 0 to 4) was calculated by assigning one point each for (1) the presence of one or more lacunes, (2) any CMB(s), (3) moderate-to-severe basal ganglia PVS, and (4) early confluent deep WMH (Fazekas 2–3) or irregular periventricular WMH (Fazekas 3) extending into the deep white matter.[17] MRI scans were processed using FreeSurfer software v6.0.0 (http://surfer.nmr.mgh.harvard.edu/) to calculate the cortical thickness; briefly, cortical thickness was defined as the minimal distance between pial and white surfaces at each vertex using the longitudinal scheme, and each hemisphere was automatically subdivided into 34 Desikan-Killiany regions for averaging.

PET acquisition and analysis

PiB was manufactured and handled according to good manufacturing practice at the PET Center, NTUH, Taipei, Taiwan (specific activity: 39±19 GBq/μmol). PET scanning was performed within 3 months of MRI. Static PET/computed tomography (CT) scans (Discovery ST; GE Healthcare, Waukesha, WI, USA) were acquired in 3-dimensional mode for 30 minutes, starting 40 minutes post-injection of 10 mCi ^{11}C-PiB. PET data were reconstructed via ordered set expectation maximization (five iterations, 32 subsets, post-filter 2.57) and corrected for attenuation. Each PiB PET image was realigned, resliced, and manually co-registered to a standardized CT template using PMOD software.[1,2,7]

PET data were expressed as the average mean standardized uptake value ratio (SUVR) of the whole cortex using the cerebellar cortex as a reference region. Areas of macrobleeds were manually excluded from SUVR analyses, and the SUVR of the affected region of interest was calculated using the ICH-free hemisphere.

Statistical analysis

Discrete variables are presented as counts (%) and continuous variables are presented as mean (±standard deviation) or median (interquartile range), depending on their distribution. Categorical variables were analyzed using Fisher's exact test, and continuous variables were analyzed using the Wilcoxon rank-sum test. Inter-rater and intra-rater reliability for evaluating CMIs were assessed using Cohen's kappa coefficient. The follow-up time for each participant was calculated from the date of the PiB PET scan to the occurrence of cognitive decline, death, or up to 5 years. Rates of cognitive decline were determined as incidence per 100-person-years. Kaplan-Meier analyses were conducted to plot the disease-free probability. Cox regression analyses were performed to estimate hazard ratios and 95% confidence intervals for cognitive decline and to compare follow-up outcomes between participants with and without CMI. All statistical analyses were performed using STATA version 18 (StataCorp., College Station, TX, USA). All tests of significance were two-tailed, with $P<0.05$ considered statistically significant.

Standard protocol approvals, registrations, and participant consent

This study was performed with the approval of the institutional review board (201903069RINB, 202210055RINA) of NTUH and in accordance with their guidelines. This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology Statement.[18] Written informed consent was obtained from all participants or their family members.

Supplementary References

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