Combined effect of cortical superficial siderosis and cerebral microbleed on short-term and long-term outcomes after intracerebral haemorrhage

Yujia Jin,1 Yu-hui Huang,2 Yu-ping Chen,1 Yao-dan Zhang,2, 1 Jiawen Li,1 Kai-cheng Yang,1 Xianghua Ye,1 Lu-hang Jin,1 Jian Wu,3 Chang-zheng Yuan,2 Feng Gao,1 Lu-sha Tong1

ABSTRACT

Background and purpose Cortical superficial siderosis (cSS) and cerebral microbleed (CMB) have distinct effects on intracerebral haemorrhage (ICH). We aim to investigate the combined effect of cSS and CMB on outcomes after ICH.

Methods Based on a single-centre stroke registry database, patients with spontaneous ICH who had CT scan within 48 hours after ictus and MRI subsequently were identified. Eligible patients were divided into four groups (cSS-CMB−, cSS-CMB+, cSS+CMB−, cSS+CMB+) according to cSS and CMB on susceptibility-weighted image of MRI. Primary outcomes were haematoma volume on admission and unfavourable outcome defined as modified Rankin Scale scores ≥3 at 3 months. Secondary outcomes were all-cause death, recurrence of stroke and ICH during follow-up (median follow-up 2.0 years, IQR 1.0–3.0 years).

Results A total of 673 patients were identified from 1044 patients with spontaneous ICH. 131 (19.5%) had CMB and 468 (69.5%) had CMB. Patients with cSS+CMB+ had the highest rate of poor outcome at 3 months, as well as all-cause death, recurrent stroke and ICH during follow-up. In cSS+ patients, CMB was associated with smaller haematoma (β = −0.13; 95% CI −0.22 to −0.03; p = 0.009), but it still increased risks of recurrent ICH (OR 4.6; 95% CI 1.3 to 15.6; p = 0.015) and stroke (OR 2.0; 95% CI 1.0 to 4.0; p = 0.049). These effects of CMB became unremarkable in the context of cSS+.

Conclusions Patients with different combinations of cSS and CMB have distinct patterns of short-term and long-term outcomes. Although CMB is related to restrained haematoma, it does not improve long-term outcomes. Trial registration number NCT04803292.

INTRODUCTION

Cortical superficial siderosis (cSS) and cerebral microbleed (CMB) are both haemorrhagic imaging biomarkers of cerebral small vessel disease (SVD). cSS is considered as previous extravasation of blood on the superficial cortex or subarachnoid space, manifesting hypointense curvilinear signal in susceptibility-weighted image (SWI) on MRI. CMB emerges as a round or ovoid signal less than 10 mm in brain parenchyma on SWI. Both of them are majorly regarded as quantifying and reflecting the severity of SVD-related haemorrhagic damage. However, the coexistence and severity of microvascular changes can affect the integrity of neurovascular unit in a network pattern, and form an ‘avalanche’ when finally intracerebral haemorrhage (ICH) happens. These two markers can also affect the enlargement of bleeding as well as haematoma elimination. Previous studies have revealed that cSS and CMB have contrary influence on haematoma volume and expansion in patients with acute-phase ICH. The presence of cSS is a strong indicator of large haematoma volume and high risk of haematoma expansion especially for lobar ICH, which usually indicates cerebral amyloid

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Many studies focused on effects of cortical superficial siderosis (cSS) and cerebral microbleed (CMB), respectively. Both of them predicted high risks of intracerebral haemorrhage (ICH) occurrence and poor outcomes. However, few data exhibited the coexistence and combination effect of CMB and cSS on short-term and long-term outcomes after spontaneous ICH.

WHAT THIS STUDY ADDS

⇒ This study suggests that different combinations of cSS and CMB predict distinct patterns of short-term and long-term outcomes. Although CMB is related to restrained haematoma, it does not benefit long-term outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These results produced by combined effect analysis fulfill clinical need more precisely and add evidence to stratified prognostic model in short-term and long-term outcomes in patients with spontaneous ICH.
angiopathy (CAA).\textsuperscript{1,6} On the contrary, absence of CMB was independently associated with large haematoma volume and haematoma expansion, regardless of ICH location (lobar or deep).\textsuperscript{1,3} These results suggest the different pathophysiological changes elicited by cSS and CMB as ‘background’ before ICH. For long-term outcomes after ICH, including stroke recurrence and mortality, both cSS and CMB appear as risk factors.\textsuperscript{1,7–15}

In this context, what kind of integrated effect will appear after ICH in patients having only cSS or only CMB or both of them? If patients with CMB appear with smaller haematoma, will they also gain better outcomes in a period of years? Despite of high prevalence of cSS and CMB of 15\%–20\% and 40\%–50\% in ICH patients as reported, data are limited regarding at the individual and combined effect of CMB and cSS on short-term and long-term outcomes after spontaneous ICH.\textsuperscript{1,3,7–16} Here, we divided patients with spontaneous ICH from a consecutive cohort into four groups according to the presence or absence of cSS and CMB: cSS-CMB\(^{-}\) (without cSS or CMB), cSS-CMB\(^{+}\) (with CMB but no cSS), cSS+CMB\(^{-}\) (with cSS but no CMB), cSS+CMB\(^{+}\) (with both cSS and CMB). Haematoma volume on admission, 90-day modified Rankin Scale (mRS), stroke recurrence and all-cause death during follow-up were chosen as short-term and long-term outcomes.\textsuperscript{17–20} The hypothesis is that outcomes differ outcomes among the four groups, and more recognition about the heterogeneity of the two haemorrhagic SVD markers would be disclosed.

**METHODS**

**Study subjects**

This study collected data from a single-centre database of patients with ICH. The protocol of enrollment has been described in our previous work.\textsuperscript{6} Briefly speaking, patients admitted within 48 hours after ICH with subsequent 3.0T MRI examination were included (figure 1). Clinical data were collected per protocol.\textsuperscript{5}

**Neuroimaging and study outcomes**

The haematoma volume in the present research was assessed on baseline CT.\textsuperscript{6} For some patients, if it was too early, for example, within 12 hours after ictus, doctors

---

**Figure 1** Flow chart. ICH, intracerebral haemorrhage; IVH, isolated intraventricular haemorrhage; MRS, modified Rankin Scale; SWI, susceptibility-weighted image.
probably would perform a repeated CT at about 24 hours later to check haematoma expansion. And in this context, we would choose the ‘stabilised’ haematoma volume (but still within 48 hours) as haematoma volume. Initial and follow-up haematoma location and volume were calculated per protocol.6 For analyses of haematoma expansion, patients who had initial CT within 24 hours and a subsequent CT in 24±6 hours thereafter were included. Haematoma expansion is defined as an increase in volume exceeding 6mL or 33% of the baseline volume.27

Patients underwent MRI during hospitalisation.6 If there were more than one MRI scan, the earliest one was chosen (median delay, 5 (IQR 4–7) days after ICH). cSS and CMB were evaluated per protocol.6 Probable CAA was evaluated according to modified Boston criteria.26 Investigators who performed all the radiological outcome assessments were blinded to clinical data.

Ninety-day mRS, all-cause death and recurrence of stroke (including ischaemic stroke and ICH) and ICH were obtained during follow-up.6 Termination of follow-up was defined as the last follow-up date before censor, or the end of the longest 3-year follow-up period, or death. We tried our best to maintain a maximum of follow-up.6

### Statistical analysis

Continuous variables are presented as mean (SD) or median (IQR) and compared by t-test or Mann-Whitney U test. Categorical variables are presented as count (per cent), and they are analysed by the Pearson χ² test or Fisher’s exact test as appropriate.

The baseline variables (demographics, vascular risk factors and past history, medication and Glasgow Coma Scale (GCS) on admission, imaging characteristics) and short-term and long-term outcomes (haematoma volume, 90-day mRS, all-cause mortality, ICH and stroke recurrence during follow-up) were compared among the four groups (cSS-CMB−, cSS-CMB+, cSS+CMB−, cSS+CMB+). A 90-day mRS was dichotomised into good and poor functional outcomes by using a cut-off of 3 (<3, ≥3). Crude and multivariable logistic regression analyses and Cox proportional hazard models were applied. Potential confounders adjusted in multivariable models included age, sex and other variables with p<0.1 in bivariate analysis as a screening criterion. Although haematoma volume and locations were both selected, regarding the underlying pathophysiological mechanisms, we did not include them in multivariable models. Collinearity and interactions could not be fully excluded for potential interactive biological pathways among cSS, CMB, haematoma volume and location. The crude cumulative survival rates in follow-up and cumulative risks of recurrent stroke for each group were shown in Kaplan-Meier plots and compared by using the log-rank test. For patients who experienced multiple recurrent stroke events during follow-up, data of stroke were censored after the first recurrent stroke event. A sensitivity analysis was conducted between groups among patients who had MRI within 1 week.

Statistical analyses were performed by using Empower (www.empowerstats.com, X&Y Solutions, Boston, Massachusetts, USA), Hiplot (ORG) (https://hiplot.org) and R (https://www.R-project.org/). A two-tailed p<0.05 was considered statistically significant. We designed this study according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.20

### RESULTS

The data analyses were performed in August 2021 though the follow-up kept on thereafter. In the cohort consisting of 1044 patients admitted within 48 hours after ICH, 673 patients went into analysis when evaluating haematoma volume, and 663 patients were included in 90-day mRS evaluation. Data of all-cause death were collected in 669 patients, and 668 patients provided information of recurrent stroke and ICH. The clinical and imaging characteristics were compared between patients included and excluded (online supplemental table 1).

#### Prevalence and characteristics of cSS and CMB

In the whole cohort, 131 of 673 (19.5%) patients presented cSS and 468 (69.5%) had CMB. Interrater agreement in classifying cases was high (kappa value 0.89, 95% CI 0.83 to 0.96 for cSS; kappa value 0.95, 95% CI 0.93 to 0.97 for CMB). The baseline characteristics and short-term and long-term outcomes among patients in different groups (cSS-CMB−, cSS-CMB+, cSS+CMB−, cSS+CMB+) were compared (table 1). Patients in cSS+CMB and cSS+CMB+ groups were older, but only cSS+CMB patients demonstrated a higher prevalence of atrial fibrillation and coronary heart disease. The cSS-CMB+ and cSS+CMB+ groups had a higher prevalence of previous ICH and ischaemic stroke or transient ischaemic attack (TIA).

Imaging characteristics of CMBs in cSS− and cSS+ patients were also diversified. Higher CMB counts were found in cSS+ patients, regardless of lobar or non-lobar area. In cSS-CMB+ group, most CMBs were observed in deep areas; whereas in cSS+CMB+ group, CMBs were majorly located in lobar areas. The highest proportion of probable CAA was found in cSS+CMB+ group (10 out of 25, 40%), followed with cSS+CMB+ group (25 out of 106, 23.6%).

#### Combined effect in haematoma volume and expansion

A total of 673 patients were included for the analysis of haematoma volume and 306 patients were included for assessing haematoma expansion. Eight patients presented more than one haematoma when the haematoma volume was assessed. Patients with cSS (cSS+CMB and cSS+CMB+) presented larger haematoma, higher proportions of lobar haematoma, haematoma expansion as well as IVH, than those without cSS (cSS-CMB− and cSS-CMB−; see table 1). Univariable and multivariable analyses for haematoma volume were performed. The presence of cSS (adjusted β, 4.5 mL; 95% CI 2.0 to 7.1) and fewer non-lobar CMBs...
Open access

Jin Y, et al. Stroke & Vascular Neurology 2023;0. doi:10.1136/svn-2023-002439

(adjusted β, −0.2 mL; 95% CI −0.3 to −0.04) were independently associated with larger haematoma volume after adjusting for age, history of hypertension, diabetes mellitus, haematoma location and intraventricular extension (online supplemental table 2 and 3). The presence of cSS would avert the ‘shrinking’ effect of over 20 non-lobar CMBs on haematoma volume (online supplemental table 3). Further stratified analysis showed that CMB counts were inversely associated with haematoma volume only in patients without cSS (adjusted β, −0.1 mL; 95% CI −0.2 to 0), and this tendency was mainly contributed by the subgroup of patients without lobar haematoma. No interactive effect was found between cSS and CMB when evaluating haematoma volume (table 2).

Table 1  Comparison of characteristics in four groups

<table>
<thead>
<tr>
<th></th>
<th>cSS–CMB− (n=180)</th>
<th>cSS–CMB+ (n=362)</th>
<th>cSS+CMB− (n=25)</th>
<th>cSS+CMB+ (n=106)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), year</td>
<td>58 (13)</td>
<td>61 (12)</td>
<td>69 (11)</td>
<td>68 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>65 (36.1)</td>
<td>125 (34.5)</td>
<td>6 (24.0)</td>
<td>41 (38.7)</td>
<td>0.557</td>
</tr>
<tr>
<td>Vascular risk factors and medical history, n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>118 (65.6)</td>
<td>298 (82.3)</td>
<td>17 (68.0)</td>
<td>76 (71.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>26 (14.4)</td>
<td>62 (17.1)</td>
<td>7 (28.0)</td>
<td>17 (16.0)</td>
<td>0.385</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3 (1.7)</td>
<td>11 (3.0)</td>
<td>3 (12.0)</td>
<td>4 (3.8)</td>
<td>0.047</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>5 (2.8)</td>
<td>15 (4.1)</td>
<td>4 (16.0)</td>
<td>3 (2.8)</td>
<td>0.015</td>
</tr>
<tr>
<td>Previous ICH</td>
<td>3 (1.7)</td>
<td>25 (6.9)</td>
<td>1 (4.0)</td>
<td>16 (15.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischaemic stroke or TIA</td>
<td>7 (3.9)</td>
<td>42 (11.6)</td>
<td>0 (0.0)</td>
<td>13 (12.3)</td>
<td>0.006</td>
</tr>
<tr>
<td>Smoking</td>
<td>61 (33.9)</td>
<td>119 (32.9)</td>
<td>11 (44.0)</td>
<td>37 (34.9)</td>
<td>0.716</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>49 (27.2)</td>
<td>112 (30.9)</td>
<td>11 (44.0)</td>
<td>37 (34.9)</td>
<td>0.269</td>
</tr>
<tr>
<td>Medication at baseline, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet drugs</td>
<td>9 (5.0)</td>
<td>37 (10.2)</td>
<td>3 (12.0)</td>
<td>9 (8.5)</td>
<td>0.209</td>
</tr>
<tr>
<td>Anticoagulant drugs</td>
<td>1 (0.6)</td>
<td>6 (1.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0.372</td>
</tr>
<tr>
<td>Antihypertension drugs</td>
<td>44 (25.3)</td>
<td>156 (45.9)</td>
<td>11 (45.8)</td>
<td>45 (45.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin</td>
<td>6 (3.3)</td>
<td>21 (5.8)</td>
<td>2 (8.0)</td>
<td>7 (6.6)</td>
<td>0.519</td>
</tr>
<tr>
<td>SBP, median (IQR)</td>
<td>159 (140–178)</td>
<td>162 (148–179)</td>
<td>154 (143–167)</td>
<td>161 (144–179)</td>
<td>0.161</td>
</tr>
<tr>
<td>DBP, median (IQR)</td>
<td>90 (80–100)</td>
<td>91 (83–102)</td>
<td>88 (78–96)</td>
<td>89 (79–99)</td>
<td>0.077</td>
</tr>
<tr>
<td>Imaging characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCT, median (IQR), hour</td>
<td>4 (2–9)</td>
<td>5 (2–7)</td>
<td>5 (4–8)</td>
<td>5 (3–9)</td>
<td>0.377</td>
</tr>
<tr>
<td>Haematoma volume, median (IQR), mL</td>
<td>9.3 (3.5–17.7)</td>
<td>7.5 (2.3–15.0)</td>
<td>15.3 (11.2–17.6)</td>
<td>10.2 (4.6–33.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICH location, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobar location</td>
<td>26 (14.4)</td>
<td>61 (16.9)</td>
<td>11 (44.0)</td>
<td>45 (42.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deep location</td>
<td>125 (69.4)</td>
<td>238 (65.7)</td>
<td>13 (52.0)</td>
<td>50 (47.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>11 (6.1)</td>
<td>31 (8.6)</td>
<td>1 (4.0)</td>
<td>10 (9.4)</td>
<td>0.597</td>
</tr>
<tr>
<td>Brainstem</td>
<td>20 (11.1)</td>
<td>47 (13.0)</td>
<td>0 (0.0)</td>
<td>5 (4.7)</td>
<td>0.030</td>
</tr>
<tr>
<td>Intraventricular extension, n (%)</td>
<td>33 (18.3)</td>
<td>94 (26.0)</td>
<td>14 (56.0)</td>
<td>51 (48.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haematoma expansion, (n%)*</td>
<td>8 (11.1)</td>
<td>18 (10.9)</td>
<td>4 (25.0)</td>
<td>11 (20.8)</td>
<td>0.137</td>
</tr>
<tr>
<td>OMT, median (IQR), day</td>
<td>5 (4–7)</td>
<td>5 (4–7)</td>
<td>6 (5–8)</td>
<td>6 (4–7)</td>
<td>0.065</td>
</tr>
<tr>
<td>Total CMB, median (IQR), n</td>
<td>4 (2–10)</td>
<td>11 (3–28)</td>
<td>5 (1–14)</td>
<td>3 (1–6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lobar CMB</td>
<td>1 (0–3)</td>
<td>5 (1–14)</td>
<td>3 (1–6)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Non-lobar CMB, n</td>
<td>3 (1–6)</td>
<td>25 (23.6)</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable CAA, n (%)</td>
<td>0 (0.0)</td>
<td>13 (3.6)</td>
<td>10 (40.0)</td>
<td>25 (23.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GCS on admission, median (IQR)</td>
<td>15 (15–15)</td>
<td>15 (14–15)</td>
<td>15 (14–15)</td>
<td>15 (13–15)</td>
<td>0.003</td>
</tr>
<tr>
<td>NIHSS, median (IQR)†</td>
<td>4 (2–9)</td>
<td>4 (2–10)</td>
<td>3 (1–8)</td>
<td>5 (2–10)</td>
<td>0.588</td>
</tr>
</tbody>
</table>

Values are mean (SD), median (IQR) or number (%) as appropriate.
*A total of 306 patients with second CT scan were included in analysis for haematoma expansion.
†NIHSS was not obtained on admission but mainly on transmission to neurology ward (usually 1–2 days after admission to emergency room).
CAA, cerebral amyloid angiopathy; CMB, cerebral microbleed; cSS, cortical superficial siderosis; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; ICH, intracerebral haemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OCT, time from onset to CT (hour); OMT, time from onset to MRI (day); SBP, systolic blood pressure; TIA, transient ischaemic attack.
Ninety-day neurological function

A total of 663 patients were consented for analysis of 90-day mRS. The presence of cSS+CMB+ was related to worse 90-day outcome when compared with those without cSS (cSS-CMB− and cSS-CMB+), either in crude model or in adjusted models (Table 3). In patients with CMB, cSS was identified as a strong predictor of poor outcome at 3 months (cSS–CMB+ vs cSS+CMB+, adjusted OR 2.0; 95% CI 1.2 to 3.3); but in patients with cSS, the addition of CMB did not increase the risk of poor 90-day outcome significantly (cSS+CMB− vs cSS+CMB+, adjusted OR 2.2; 95% CI 0.7 to 6.8; online supplemental table 4). Multivariable analyses showed that independent characteristics associated with worse 90-day mRS were increasing age, intraventricular extension, the presence of cSS and low GCS on admission. The occurrence and counts of CMB elicited an unremarkable effect on 90-day outcome (online supplemental table 4 and 5). The distribution of 90-day mRS among the four groups can be seen in figure 2.

All-cause death

As of August 2021, during 1436 person-years of follow-up (median follow-up 2.0 years, IQR 1.0–3.0 years), 59 out of 669 patients (9%) died during follow-up. The causes of death included: ICH (16 died of initial ictus and 12 died of recurrent ICH), recurrent ischaemic stroke (3), unclassified cerebrovascular events (2), myocardial infarction (2), complication owing to epilepsy (1), complication due to bone fracture (2), complication due to malignant tumours (3), pulmonary embolism (1), renal failure (1) and ambiguous causes of death (16). The cSS+CMB+ group developed the highest incidence rate of death (figure 3). In patients with CMB, the presence...
of cSS was associated with a higher risk of death; while in patients with cSS, the presence of CMB did not increase risk of death significantly (table 4).

**Recurrent stroke and ICH**

Eighty-four out of 668 patients (12%) experienced recurrent stroke and 47 patients (7%) had ICH recurrence during follow-up. In patients with CMB, the presence of cSS increased the risk of recurrent ICH (cSS-CMB+ vs cSS+CMB+, crude HR 2.2; 95% CI 1.2 to 4.2), but it became non-significant after adjusting for age, sex, history of hypertension, atrial fibrillation, coronary heart disease, previous ICH, ischaemic stroke or TIA, smoking, alcohol intake, GCS on admission (table 4). In patients with cSS, the presence of CMB did not increase the risk of recurrent stroke or ICH (cSS+CMB− vs cSS+CMB+, table 4). The crude cumulative incidence rates of recurrent stroke and ICH in four groups were shown in figure 4.

**Patients with single CMB**

In this study, 88 patients (13.1%) had single CMB and were considered as CMB+. We performed additional analysis regarding single CMB as CMB−. The results were consistent with analysis that marked single CMB as CMB+. For the outcome of 90-day mRS, recurrent stroke and ICH, as well as all-cause death, cSS+CMB+ patients still presented the worse outcomes compared with cSS-CMB− patients (online supplemental table 6 and 7).

**Sensitivity analysis**

Sensitivity analysis included 550 (81.7%) patients who had MRI within 1 week after ICH ictus. Non-lobar CMB is inversely associated with haematoma volume (online supplemental table 3). cSS+CMB+ group still had the highest ratio of unfavourable outcome at 3 months, all-cause death and recurrent stroke, but was second to cSS+CMB− as to ICH recurrence (online supplemental figure 1-4).

We reran the main statistical tests with our recorded National Institutes of Health Stroke Scale (NIHSS) in supplement materials (online supplemental table 8 and 9). And for the colinear concern, we eliminated GCS this time, and the results were consistent with our previous tests.

**DISCUSSION**

In this prospective cohort with spontaneous ICH, cSS can be observed in every one of five patients and almost 70% patients displayed CMB, which showed a higher prevalence of CMB compared with other reported ICH cohorts. In this study, combined effects of CMB and cSS on short-term and long-term outcomes were analysed by dividing the cohort into four groups, cSS-CMB−, cSS-CMB+, cSS+CMB−, cSS+CMB+. Coexistence of cSS and CMB was observed in 15.8% patients and developed the highest incidence rate of poor outcome at 3 months, all-cause death, stroke and ICH recurrence in a median follow-up of 2.0 years. Regarding haematoma volume, especially in patients without cSS, an inverse relationship between CMB and ICH volume was disclosed and was furtherly found count-dependent. However, for long-term outcomes, CMB brought about a noxious effect on stroke and ICH recurrence in cSS− groups during follow-up, though this effect was statistically unremarkable between cSS+ groups.

The study illustrated that cSS and CMB exerted distinct effects on short-term and long-term outcomes after ICH. Intriguingly, although CMB was inversely associated with haematoma volume, especially in non-lobar haemorrhage, patients with CMB still ended up with a higher risk of death, stroke and ICH during follow-up. These results were in line with previous mechanism researches and cohort studies focusing on cSS or CMB, respectively. We reinforced the previous findings indicating that cSS and CMB were different entities in pathogenesis mechanisms. Moreover, our findings...
implicated that there were other critical factors residing in the relationship between CMB and long-term outcome after index ICH besides initial haematoma volume. Based on prior research, these critical factors could be chronic destruction of cerebral functional integrity and network, such as dementia, depression and systemic organ decline, which are independent of ICH recurrence in cSS+ patients, especially in CAA cohorts.33–39

Previous cohort studies focusing on cSS reported that the risk of recurrent ICH would increase in patients with disseminated cSS (≥3 sulci), but not in patients with focal cSS (<3 sulci).7 A meta-analysis of prospective cohorts

Table 4 Outcomes compared in CMB+ and cSS+ groups

<table>
<thead>
<tr>
<th></th>
<th>CMB+</th>
<th>CMB+</th>
<th>CMB−</th>
<th>CMB+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=362)</td>
<td>(n=106)</td>
<td>(n=25)</td>
<td>(n=106)</td>
</tr>
<tr>
<td>Crude model</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome</td>
<td>OR (95% CI)</td>
<td>P value</td>
<td>OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>90-day mRS≥3</td>
<td>2.0 (1.2 to 3.3)</td>
<td>0.007</td>
<td>2.2 (0.7 to 6.8)</td>
<td>0.180</td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause death</td>
<td>Reference</td>
<td>1.9 (1.0 to 3.4)</td>
<td>0.043</td>
<td>Reference</td>
</tr>
<tr>
<td>Recurrent ICH</td>
<td>Reference</td>
<td>1.7 (0.8 to 3.3)</td>
<td>0.143</td>
<td>Reference</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>Reference</td>
<td>1.7 (1.0 to 2.9)</td>
<td>0.034</td>
<td>Reference</td>
</tr>
<tr>
<td>Adjusted model*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome</td>
<td>OR (95% CI)</td>
<td>P value</td>
<td>OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>90-day mRS≥3</td>
<td>2.0 (1.2 to 3.3)</td>
<td>0.007</td>
<td>2.2 (0.7 to 6.8)</td>
<td>0.180</td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause death</td>
<td>Reference</td>
<td>1.9 (1.0 to 3.4)</td>
<td>0.043</td>
<td>Reference</td>
</tr>
<tr>
<td>Recurrent ICH</td>
<td>Reference</td>
<td>1.7 (0.8 to 3.3)</td>
<td>0.143</td>
<td>Reference</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>Reference</td>
<td>1.7 (1.0 to 2.9)</td>
<td>0.034</td>
<td>Reference</td>
</tr>
</tbody>
</table>

*Adjusted by age, sex, history of hypertension, atrial fibrillation, coronary heart disease, previous ICH, ischaemic stroke or TIA, smoking, alcohol intake, GCS on admission.

CMB, cerebral microbleed; cSS, cortical superficial siderosis; GCS, transient ischaemic attack; ICH, intracerebral haemorrhage; mRS, modified Rankin Scale; TIA, transient ischaemic attack.

Figure 4 Cumulative hazard of recurrent stroke (A) and intracerebral haemorrhage (B) during follow-up. CMB, cerebral microbleed; cSS, cortical superficial siderosis.
including 1306 patients with ICH discovered that CMB≥2 in CAA-related and >10 in CAA-unrelated ICH was associated with a higher ICH recurrence risk. Clinically, we have readily met patients with different combinatorial patterns of cSS and CMB. We tried to quantify the combined effects of cSS and CMB in this ICH cohort. For haematoma volume, cSS inverted the ‘shrinking’ effect equivalent to over 20 non-lobar CMBs (online supplemental table 3), whereas for the long-term outcomes, cSS presented an overwhelmingly noxious effect over CMB. These results will fulfil clinical need more precisely and could provide stratified potential risks in short-term and long-term outcomes in patients with spontaneous ICH. In the context of extensive application of anticoagulation and antiplatelet therapies nowadays, individualised evaluation of short-term and long-term risks will be especially important. As to single CMB, literature showed inconsistent results for patients with a single CMB. The clinical significance is uncertain because it may indicate a less severe microangiography compared with multiple CMBs. Rating of a single CMB according to MRI is also less reliable. Thus, we additionally performed analysis regarding patients with a single CMB as CMB−, and found the main results remained consistent with previous analysis.

Recent researches provided evidence that cSS and CMB have different imaging distribution characteristics and correlations with APOE genotypes. The hypothesis is that cSS and CMB have partially distinct vasculopathic mechanisms, even in CAA. cSS, especially disseminated cSS, has a strong correlation with APOE ε2+genotype. CAA-related vasculopathic changes and fragility associated with APOE ε2+allele may have a biologically meaningful role in the pathophysiology and severity of cSS. CMB (especially patients with strictly lobar CMBs), on the other hand, is more relevant to APOE ε4+that appears to enhance vascular Aβ deposition in a dose-dependent fashion, and probably promotes CAA-related vessel thickening and induces microvascular intraparenchymal haemorrhage (eg, strictly lobar CMBs). In contrast, APOE ε2+might be related to severe stages or aggressive phenotype of CAA pathology (eg, vessel cracking, vessel-within-vessel appearance and fibrinoid necrosis) that result in vessel rupture, especially in leptomeningeal vessels, hence contributing to cSS and CAA-related ICH and large ICH volume. Meanwhile, there is evidence suggesting that APOE ε4+ is associated with CAA type 1 (with cortical capillary Aβ deposition) and APOE ε2+ is associated with CAA type 2 (without cortical capillary Aβ involvement but probably larger size of meningeal vessels). Numerous clinical studies and laboratory information have shown that ICH is a highly heterogeneous disease with varied genotype polymorphism. Our results underline the importance of a more detailed imaging clinical classification of ICH which can contribute to more accurate individualised treatment.

We are aware of some limitations. We excluded patients with surgical procedures and patients without MRI during hospitalisation. Patients would not obtain an MRI scan if they had a pacemaker, prosthetic heart valve, severe neurological impairment, unstable vital signs, etc. Therefore, it is noteworthy that patients included in this study had relatively mild ICH. This explains why patients in this study had higher GCS on baseline and ended up with better outcomes compared with other studies. This limitation is obvious but hard to ameliorate in studies requiring MRI. Meanwhile, we are aware of the limitation of not including NIHSS as a more detailed neurological assessment on admission. Baseline clinical severity is indeed strongly associated with functional outcomes. But regrettably, patients with spontaneous ICH were admitted into the emergency room and only recorded GCS on admission. When we evaluate the NIHSS, it was 1–2 days later, and thus did not fit the definition of NIHSS on admission. Therefore, we did not include it in the main analyses. However, we reran the main statistical tests with our recorded NIHSS in supplement materials. And for the colinear concern, we eliminated GCS this time, the results were consistent with our previous tests (see online supplemental table 8 and 9). In the present single-centre cohort study of 673 patients, the cSS+CMB− group consisted of 25 patients only. The small sample size and imbalance among subgroups may restrain the statistical efficacy, and could lead to the false positive results on long-term endpoints when compared with cSS+CMB+ patients. Considering the insufficient sample size, multiple comparisons and population bias, the high probability of type 1 error should be noticed. We provided multivariable model that only adjusted age and sex in online supplemental table 10 and 11. Larger cohorts with multicentres are encouraged to test these results in future. Finally, another limitation was the lack of cognition and mental assessments, which were also found to be critical factors other than stroke events associated with long-term outcomes recently. 

CONCLUSIONS

Our study suggests that patients with different combinations of cSS and CMB have distinct patterns of short-term and long-term outcomes, which will be especially exacerbated when cSS and CMB appear simultaneously. Although patients with CMB might have restrained haematoma, it does not predict favourable long-term outcomes.

Contributors Concept and design: L-ST, FG and YJ. Acquisition, analysis or interpretation of data: YJ, C-ZY, JL, XY, L-HJ, JW and Y-PC. Drafting of the manuscript: YJ. Critical revision of the manuscript for important intellectual content: L-ST, FG and YJ. Statistical analysis: YJ, Y-HH, Y-DZ and K-CY. Obtained funding: L-ST and FG. Administrative, technical or material support: L-ST, Y-PC, Y-HH and Y-DZ. Supervision and Guarantor: L-ST, FG, C-ZY, Y-J and Y-HH contributed equally to the manuscript; L-ST and FG are both corresponding authors.

Funding The work was supported by grants from National Natural Science Foundation of China (NSFC) 81871615, 81971515, 81971516 and 81500991, and the Science and Technology Department of Zhejiang Province (2022KY174), and ‘Leading Goose’ R&D Program of Zhejiang (2023C03026).

Competing interests None declared.
Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the study protocol was considered observational by the internal review board of the 2nd Affiliated Hospital of Zhejiang University, School of Medicine (ID: I20200011153). Written informed consent was obtained from patients or their relatives for data collection and follow-up. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Data are presented within the article and online supplemental materials. Additional information can be obtained on request to the corresponding author.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omission arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Yujia Jin http://orcid.org/0000-0002-7876-6028
Yao-dan Zhang http://orcid.org/0000-0001-9787-7017
Jiawen Li http://orcid.org/0000-0002-2689-0710

REFERENCES


