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1     **Development of a stroke risk score with MRI asymptomatic brain lesions**  
2                     **attributes to evaluate prognostic vascular events**

3  
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11    **Short title:** A Stroke risk score with MRI findings.

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1 **Abstract**

2 **Background:** The use of a combination of stroke predictors, such as clinical  
3 factors and asymptomatic lesions on brain magnetic resonance imaging (MRI),  
4 may improve the accuracy of stroke risk prediction. Therefore, we attempted to  
5 develop a stroke risk score for healthy individuals.

6 **Methods:** We investigated the presence of cerebral stroke in 2365 healthy  
7 individuals who underwent brain dock screening at the Health Science Center in  
8 Shimane. We examined the factors that contributed to stroke and attempted to  
9 determine the risk of stroke by comparing background factors and MRI findings.

10 **Results:** The following items were found to be significant risk factors for stroke:  
11 age (  $\geq 60$  years), hypertension, subclinical cerebral infarction, deep white matter  
12 lesion, and microbleeds. Each item was scored with 1 point, and the hazard ratios  
13 for the risk of developing stroke based on the group with 0 points were 17.2 (95%  
14 confidence interval [CI] 2.31–128) for 3 points, 18.1 (95% CI 2.03–162) for 4 points,  
15 and 102 (95% CI 12.6–836) for 5 points.

16 **Conclusions:** A precise stroke prediction score biomarker can be obtained by  
17 combining MRI findings and clinical factors.

18

19 **Keywords:**

20 MRI, Stroke, Prediction, Microangiopathy, Hypertension, ischemia

21 **Abbreviations:**

22 MRI: magnetic resonance imaging

23 SWAMP: Silent brain infarction, White Matter Lesion, Age, Microbleeds, Pressure  
24 score

1 **Introduction**

2 Because the evaluation of vascular risk factors is not always enough for primary  
3 stroke prevention, asymptomatic brain lesions in MRI have attracted attention  
4 recently. Specifically, clinical vascular risk factors include hypertension<sup>1)</sup>, diabetes  
5 mellitus<sup>2)</sup>, and dyslipidemia<sup>3)</sup>, while asymptomatic brain MRI lesions include  
6 asymptomatic cerebral infarction<sup>4)</sup>, deep white matter lesions<sup>5)</sup>, and microbleeds<sup>6)</sup>,  
7 <sup>7)</sup>. Although many of these asymptomatic brain lesions are known to be associated  
8 with the previously mentioned clinical risks, especially hypertension,<sup>8)</sup> <sup>9)</sup>, no  
9 reports are indicating the risk of the first stroke occurrence when the clinical risk  
10 of vascular damage is combined with the risk revealed by MRI. In the present study,  
11 we extracted risk factors from first-ever stroke cases among participants who  
12 underwent a brain health check-up and combined them to develop a new  
13 prediction score for the stroke onset.

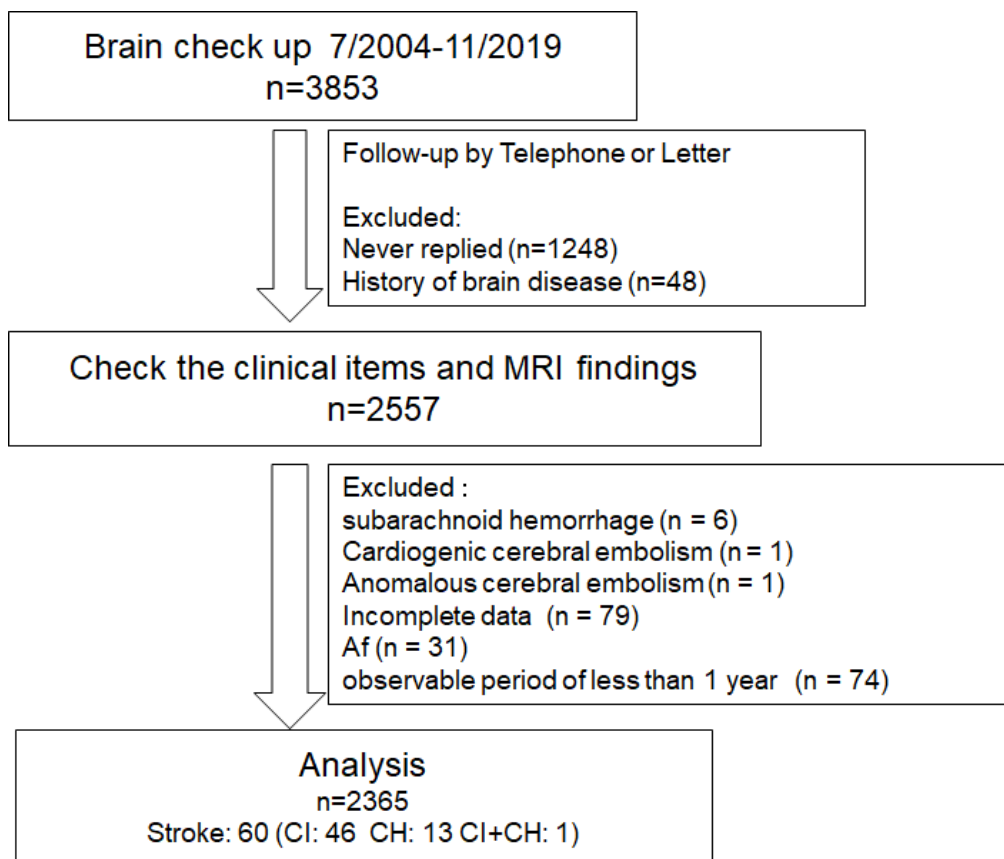
14  
15 **Methods**

16 **Study dataset**

17 This study was approved by the Medical Ethics Committee of Shimane University  
18 School of Medicine, and written consent was obtained from all participants  
19 (Approval No. 2225, Approval date: May 12, 2016). The conducted procedures  
20 were in accordance with the institutional guidelines and the Declaration of Helsinki.  
21 The participants were 3853 volunteers who underwent brain dock examination at  
22 the Health Science Center Shimane between July 14, 2004, and November 27,  
23 2019. Brain dock is a type of medical examination conducted in Japan, which is a  
24 program to perform head MRI and other tests for the purpose of primary

1 prevention or early detection of brain diseases in healthy subjects. Participants  
2 with a history of symptomatic stroke or other brain diseases, such as head injuries  
3 or brain tumors, at the time of the brain dock examination, were excluded (48  
4 participants). The occurrence of stroke after the brain scan were investigated by a  
5 follow-up survey. The last day of the study was May 14, 2021. The survey method  
6 involved the dispatch of a letter with an enclosed questionnaire to the participants  
7 who had undergone yearly brain checkups that aimed to ascertain whether or not  
8 a stroke had occurred and to determine the status at that time, based on the  
9 contents of the reply. If the details of the stroke were unknown, we confirmed the  
10 details by telephone. 1248 participants were excluded from the survey because  
11 they did not reply. Stroke types were classified into cerebral infarctions (including  
12 transient ischemic attacks) and cerebral hemorrhage, and those who had  
13 subarachnoid hemorrhage (six participants) were excluded from the analysis.  
14 Cardiogenic cerebral embolism (one participant) and anomalous cerebral  
15 embolism (one participant) were also excluded because their risk was different  
16 from that of other strokes. In addition, participants with incomplete data on the risk  
17 factors were excluded owing to a lack of reliability (79 participants). Participants  
18 with atrial fibrillation (31 participants) were excluded. Furthermore, those with an  
19 observable period of less than 1 year were excluded from the analysis (74  
20 participants), except for those who had a stroke (one participant with cerebral  
21 hemorrhage and two participants with cerebral infarction) during the observable  
22 period. After these exclusions, a total of 2365 participants were finally included in  
23 the analysis (Fig. 1). The participants were divided into two groups: those who had  
24 a stroke during follow-up, and those who did not have a stroke. The mean follow-

1 up period from the first visit to the final survey was  $8.9 \pm 4.5$  years (minimum 0.36  
2 years, maximum 16.5 years).



3

### Figure 1. Follow-up and exclusion criteria

We followed up all participants except those who had a history of brain disease among those who took the Brain check-up and analyzed the 2365 participants who responded and met the criteria adequately. 60 participants developed stroke during follow-up.

CI : cerebral infarction, CH: cerebral hemorrhage

4

### 5 Independent data access and analysis

6 The corresponding author had full access to all the data in the study and takes  
7 responsibility for its integrity and for the data analysis.

8

### 9 Evaluation of risk factors for small vessel disease

1 Age at the examination, gender, presence or absence of hypertension, diabetes  
2 mellitus, and dyslipidemia were evaluated as entered into the Brain Checkup  
3 Database. Hypertension was defined as systolic blood pressure  $\geq 140$  mmHg or  
4 diastolic blood pressure  $\geq 90$  mmHg, or a history of hypertension, or medication  
5 used for hypertension. Participants with diabetes mellitus were defined as those  
6 who had a fasting blood glucose of 126 mg/dL or higher, or who used diabetic  
7 drugs. Dyslipidemia was defined as a fasting triglyceride level of 150 mg/dL or  
8 higher, low-density-lipoprotein-cholesterol levels  $\geq 140$  mg/dL or higher, high-  
9 density-lipoprotein-cholesterol levels  $< 40$  mg/dL, or being on medication for  
10 dyslipidemia.

11

## 12 **Brain imaging evaluation**

13 Longitudinal relaxation (T1)-weighted, transverse relaxation (T2)-weighted, T2\*-  
14 weighted, and fluid-attenuated inversion recovery images were acquired in axial  
15 sections with a slice thickness of 7 mm. Asymptomatic cerebral infarction, deep  
16 white matter lesion, and microbleeds were determined according to the Guidelines  
17 for Brain Docs 2019 published by The Japan Brain Doc Society. For deep white  
18 matter lesions, a positive result was obtained if the lesion met one of the following  
19 criteria: Deep Subcortical White Matter Hyperintensity (DSWMH) 2 degree or  
20 higher according to the Fazekas classification<sup>10)11)</sup>.

21

## 22 **Statistical analysis**

23 Considering that the mean and median ages of the total samples were 61 and 62  
24 years, respectively, the participants were divided into two groups: those over 60

1 years old, and those under 60 years old. Given that the other items were also  
2 dichotomous, Pearson's chi-square test was used to examine whether there were  
3 differences in each factor between the two groups of stroke-onset and non-stroke-  
4 onset participants. For each factor that yielded significant differences between the  
5 two groups, Cox regression analysis was used to determine the hazard ratio for  
6 stroke occurrence by considering the time until stroke onset. The hazard ratios for  
7 stroke were also calculated by Cox regression analysis when multiple factors were  
8 combined. All statistical procedures were performed using IBM SPSS Statistics  
9 (version 22).  $P < 0.05$  was considered a significant difference.

10

## 11 **Results**

12 Among the 2365 participants, 60 (2.5%) had stroke, 46 had cerebral infarction, 13  
13 had cerebral hemorrhage, and one had simultaneous cerebral infarction and  
14 hemorrhage. Five significant risk factors for stroke were advanced age,  
15 hypertension, asymptomatic cerebral infarction, deep white matter lesion, and  
16 microbleeds. Conversely, gender, diabetes mellitus, and dyslipidemia did not differ  
17 between the stroke-onset and non-stroke-onset groups (Table. 1).

18



|                                |                               | Non-Stroke Group           | Stroke Group       | P-Value          | OR               | 95%CI               |
|--------------------------------|-------------------------------|----------------------------|--------------------|------------------|------------------|---------------------|
| Variable                       |                               | N = 2305                   | N = 60             |                  |                  |                     |
| Clinical Features              | Sex, n (% male)               | 1226 (53.2)                | 39 (65.0)          | 0.088            | 1.63             | 0.96 — 2.80*        |
|                                | Advanced age, n (% over 60 y) | <b>1400 (60.7)</b>         | <b>49 (81.7)</b>   | <b>&lt;0.001</b> | <b>2.88</b>      | <b>1.49 — 5.57</b>  |
|                                | Age, y                        | <b>61.8 ±10.9</b>          | <b>66.5 ±9.03</b>  | <b>&lt;0.001</b> | —                | <b>1.91 — 7.49</b>  |
|                                | Hypertension, n (%)           | <b>1321 (57.6)</b>         | <b>49 (81.7)</b>   | <b>&lt;0.001</b> | <b>3.28</b>      | <b>1.70 — 6.35*</b> |
|                                | SBP, mmHg                     | <b>128.1 ±17.8</b>         | <b>135.8 ±18.5</b> | <b>0.001</b>     | —                | <b>3.06 — 12.2</b>  |
|                                | DBP, mmHg                     | 73.4 ±11.2                 | 76.0 ±9.9          | 0.081            | —                | -0.31 — 5.41        |
|                                | Diabetes, n (%)               | 271 (11.8)                 | 12 (20.0)          | 0.067            | 1.87             | 0.98 — 3.58*        |
|                                | HbA1c, %                      | 5.49 ±0.65                 | 5.57 ±0.91         | 0.46             | —                | -0.15 — 0.33        |
|                                | sCr, mg/dL                    | 0.74±0.19                  | 0.76±0.18          | 0.43             | —                | -0.03 — 0.07        |
|                                | Dyslipidemia, n (%)           | 1388 (60.2)                | 38 (63.3)          | 0.69             | 1.14             | 0.67 — 1.94*        |
|                                | TG, mg/dL                     | 115.2 ±71.7                | 131.6 ±91.1        | 0.082            | —                | -2.08 — 35.0        |
|                                | LDL-C, mg/dL                  | 122.4 ±29.8                | 117.7 ±26.2        | 0.23             | —                | -12.3 — 2.93        |
|                                | HDL-C, mg/dL                  | 62.7 ±16.2                 | 59.1 ±17.6         | 0.083            | —                | -7.86 — 0.48        |
|                                | MRI findings                  | White Matter Lesion, n (%) | <b>650 (28.2)</b>  | <b>32 (53.3)</b> | <b>&lt;0.001</b> | <b>2.91</b>         |
| Silent Brain Infarction, n (%) |                               | <b>124 (5.4)</b>           | <b>11 (18.3)</b>   | <b>&lt;0.001</b> | <b>3.95</b>      | <b>2.00 — 7.78*</b> |
| Microbleeds, n (%)             |                               | <b>147 (6.4)</b>           | <b>11 (18.3)</b>   | <b>0.002</b>     | <b>3.30</b>      | <b>1.68 — 6.47*</b> |

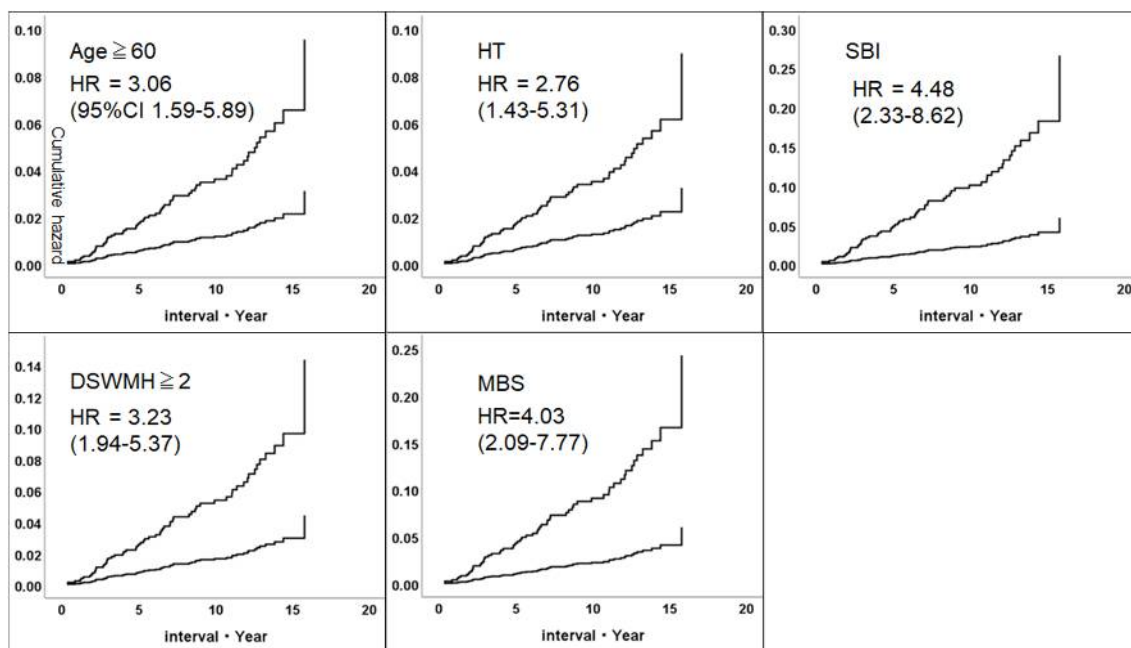
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**Table 1 Demographic and Clinical Characteristics**

OR: Odds Ratio, 95%CI: 95%Confidence Interval, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, sCr: Serum Creatinine, TG: Triglyceride, LDL-C: LDL-Cholesterol, HDL-C: HDL-Cholesterol, \*: 95% CI for Odds Ratio (Others are 95% CI for differences ), significant items (p < 0.05) are in bold. For continuous variables, mean and standard deviations are reported.

- 2 The hazard ratios for stroke occurrence were calculated by Cox regression  
3 analysis for each factor judged to be significant: 3.06 (95% CI 1.59–5.89) for age  
4 over 60 years, 2.76 (95% CI 1.43–5.31) for hypertension, 3.23 (95% CI 1.94–5.37)

1 for deep white matter lesions, 4.06 (95% CI 1.94–5.37) for asymptomatic cerebral  
2 infarction, 4.48 (95% CI 2.33–8.62), and 4.03 (95% CI 2.09–7.77) for  
3 microhemorrhage (Fig. 2).



4

**Figure 2. Stroke hazard ratios for each factor**

COX regression analysis of participants who developed stroke during follow-up showed that older age, presence of hypertension, silent brain infarction, severe deep white matter lesion (DSWMH  $\geq 2$ ), and microbleeds were predicted risk factors. Hazard ratios for each factor are shown. HT: Hypertension, WML: White Matter Lesion, SBI: Silent Brain Infarction, MBs: Microbleeds, HR: Hazard Ratio, 95%CI: 95% Confidence Interval.

5

6 **Silent brain infarction, white matter lesion age, microbleeds, pressure**  
7 **(SWAMP) score**

8 Fig. 2 shows the change over time in the cumulative incidence of stroke for each  
9 factor.

1 In order to provide an integrated risk prediction, we assigned one point to each  
 2 factor and added them together, termed as SWAMP score. The frequency of onset  
 3 and interval over the entire period for each SWAMP score is shown in Table 2.

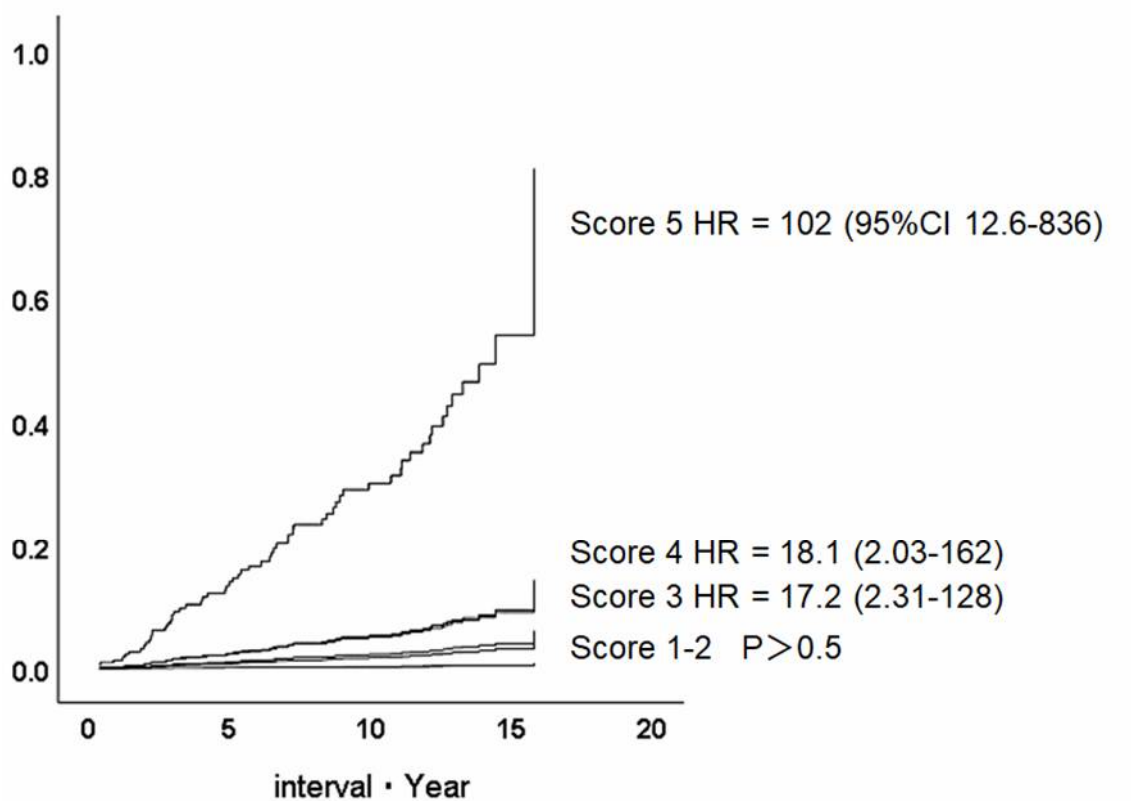
| SWAMP score | stroke | n (%)     | Interval • Year |      |         |         |        |
|-------------|--------|-----------|-----------------|------|---------|---------|--------|
|             |        |           | mean            | SD   | minimum | maximum | median |
| 0           | (-)    | 416 (100) | 7.74            | 4.37 | 1.00    | 16.47   | 7.18   |
|             | (+)    | 0 (0)     | null            | null | null    | null    | null   |
| 1           | (-)    | 684 (98)  | 9.79            | 4.21 | 1.07    | 16.49   | 10.44  |
|             | (+)    | 13 (2)    | 8.07            | 4.78 | 0.36    | 15.79   | 8.44   |
| 2           | (-)    | 660 (98)  | 9.12            | 4.52 | 1.02    | 16.52   | 9.86   |
|             | (+)    | 15 (2)    | 6.44            | 3.55 | 1.93    | 12.56   | 5.11   |
| 3           | (-)    | 419 (95)  | 8.92            | 4.60 | 1.04    | 16.47   | 9.07   |
|             | (+)    | 21 (5)    | 5.60            | 4.27 | 0.38    | 13.85   | 3.97   |
| 4           | (-)    | 100 (96)  | 6.95            | 4.15 | 1.11    | 16.38   | 6.15   |
|             | (+)    | 4 (4)     | 6.77            | 2.45 | 4.02    | 9.93    | 6.57   |
| 5           | (-)    | 26 (79)   | 7.41            | 3.92 | 1.47    | 14.24   | 6.92   |
|             | (+)    | 7 (21)    | 5.09            | 4.76 | 1.19    | 14.42   | 2.75   |
| total       | (-)    | 2305 (97) | 8.92            | 4.47 | 1.00    | 16.52   | 9.19   |
|             | (+)    | 60 (3)    | 6.36            | 4.18 | 0.36    | 15.79   | 5.53   |

4

**Table 2. Overall stroke frequency and interval by SWAMP score**

SD: standard deviation

5 The hazard ratios for stroke occurrence based on the group with a total SWAMP  
 6 score of 0 are shown in Fig. 3. Because there was no stroke case in the group  
 7 with SWAMP score of 0, one hypothetical case of stroke (cerebral infarction) was  
 8 assumed to have occurred 8.9 years after this analysis.



1

**Figure. 3 Cumulative hazard of stroke by SWAMP score**

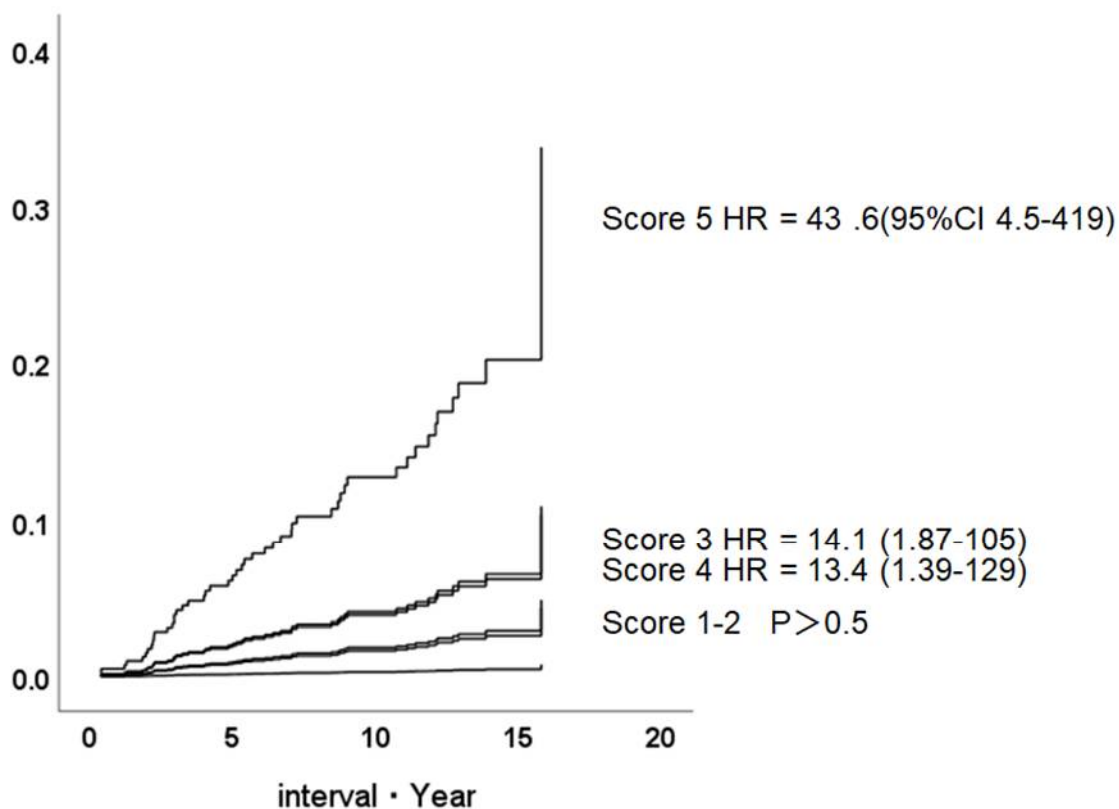
Cox regression analysis shows the hazard ratio for stroke occurrence for each score (SWAMP) with 1 point for each item in Figure 2. 3 or more points significantly increases the risk of stroke occurrence compared to score 0. HR: Hazard Ratio, 95%CI: 95% Confidence Interval.

2

3 Hazard ratios tended to increase with higher scores, particularly 17.2 (95% CI  
4 2.31–128) for 3 points, 18.1 (95% CI 2.03–162) for 4 points, and 102 (95% CI  
5 12.6–836) for 5 points, thus indicating that the risk of stroke increased significantly  
6 with higher scores.

7 In addition, Cox analysis of the data of 2352 participants, excluding 13  
8 participants with cerebral hemorrhage, showed that the hazard ratios were 14.2  
9 (95% CI 1.89–107) for 3 points, 13.6 (95% CI 1.41–131) for 4 points, and 49.2

1 (95% CI 5.12–473) for 5 points, respectively, for the incidence of ischemic stroke.  
2 The score was also effective for prognosing the development of ischemic stroke  
3 (Fig. 4).



4 **Figure. 4 Cumulative hazard of ischemic stroke by SWAMP score**

Cox regression analysis showed the hazard ratio for developing ischemic stroke for each SWAMP score compared to score 0. As with overall stroke occurrence, a score of 3 or higher significantly increased the risk of stroke occurrence. HR: Hazard Ratio, 95%CI: 95% Confidence Interval HR: Hazard Ratio, 95%CI: 95% Confidence Interval.

5  
6 **Prognostic significance of antihypertensive medications in the high-risk**  
7 **group (SWAMP scores  $\geq 3$ )**

8 To examine whether blood pressure control is effective in participants with  
9 SWAMP scores  $\geq 3$ , a t-test was performed on blood pressure at the time of visit

1 between stroke sufferers (30 participants) and non-stroke sufferers (518  
2 participants) among the 548 participants with SWAMP scores  $\geq 3$  or higher and  
3 hypertension. No differences were found. In addition, the systolic blood pressures  
4 at the time of the brain checkup were classified as 140 mmHg or higher or lower,  
5 and the prognosis of stroke was compared by Cox analysis, which also showed  
6 no significant difference. The analysis of diastolic blood pressure in the groups  
7 with diastolic blood pressure  $\geq 90$  mmHg and those with diastolic blood pressure  
8  $< 90$  mmHg also showed no significant differences.

9

## 10 **Discussion**

11 The present study has enabled us to score the risk of stroke in more detail by  
12 using asymptomatic brain lesions detected in MRI as a risk factor for stroke in  
13 addition to the conventional risk factors for vascular disease. It is already well  
14 known that asymptomatic brain lesions on MRI are a strong risk factor for the  
15 future occurrence of stroke. However, in clinical stroke cases, the presence of  
16 asymptomatic brain lesions has generally been pointed out after the stroke onset.  
17 The brain health checkup system that has become widespread in Japan has  
18 revealed that asymptomatic brain lesions occur in many healthy individuals and  
19 that these lesions might be predictive of future strokes. In the primary prevention  
20 of stroke, control of lifestyle-related diseases, such as hypertension and diabetes,  
21 has always been emphasized, while detection of asymptomatic brain lesions has  
22 not been taken into account sufficiently for stroke prevention. We developed the  
23 present score based on the belief that the use of asymptomatic brain lesions in  
24 addition to conventional vascular risk may enable more detailed risk management

1 when considering the primary prevention of stroke. As expected, the presence of  
2 asymptomatic cerebral infarction, deep white matter lesions, and microbleeds,  
3 significantly increase the risk of stroke compared with age and hypertension alone.  
4 The overlapping lesions also significantly increased the risk of stroke. Conversely,  
5 it is well known that the risk factors listed in this study are related to each other. In  
6 particular, previous reports have indicated that asymptomatic cerebral infarction,  
7 deep white matter lesions, and microbleeds are causally related to aging and  
8 hypertension<sup>8), 9), 12)</sup>. Therefore, the score can be used to reflect the severity of  
9 cerebral microvascular disease.

10 In terms of the incidence of stroke per SWAMP score and the interval between  
11 each group (Table 2), SWAMP 3 and 4 showed similar results, as did the results  
12 for these hazard ratios, which is likely due to the limited sample size.

13 Also, the 95% CIs were very broad overall. The prognostic stroke group was small  
14 (60 cases out of a total of 2365), and in this study, one hypothetical case was  
15 placed because there were no cases of stroke in the score 0 group, so an accurate  
16 risk comparison analysis could not be performed. It is assumed that these factors  
17 led to a larger 95% CI for the hazard ratios.

18 Given that the present study is based on the data of a retrospective survey of  
19 participants who underwent a brain scan, the appropriateness of applying the  
20 results to a wide range of participants is problematic in general. In this regard, the  
21 stroke incidence rate estimated for an average follow-up period of 8.9 years using  
22 the present data is 2.5%, which translates into an annual incidence rate of  
23 approximately 281 per 100000. This is in agreement with the previously reported  
24 epidemiological data<sup>13), 14)</sup>, and indicates that there is no specificity or bias in the

1 present population. The hazard ratios calculated for each asymptomatic brain  
2 lesion (deep white matter lesion: 3.23, asymptomatic cerebral infarction: 4.48,  
3 microbleeds: 4.03) were also similar to those reported previously (deep white  
4 matter lesion: 3.6<sup>4</sup>), asymptomatic cerebral infarction: 3.9<sup>4</sup>), microbleeds: 4.5<sup>6</sup>).  
5 Given that the hazard ratios were different for each factor, the scores could have  
6 been weighted to reflect their differences. In this case, the score for each individual  
7 would be a real (non-natural) number. However, we did not adopt weighting in this  
8 study because we believe that scores used in clinical practice should be  
9 expressed in terms of natural numbers. It remains to be determined whether each  
10 score should be treated as one and the same as in the present study. Furthermore,  
11 it may be necessary in the future to consider the number of asymptomatic cerebral  
12 infarctions and microbleeds. Although the present score was simplified for ease of  
13 use, it may be improved in the future when the number of participants in the study  
14 population increases. An additional limitation of this study is the fact that it was  
15 difficult to determine the type of stroke. Subarachnoid hemorrhages and  
16 cardiogenic cerebral embolisms were excluded, but lacunar infarction and  
17 atherothrombotic cerebral infarction could not be differentiated. In addition, most  
18 of the cerebral hemorrhages were deemed hypertensive cerebral hemorrhages  
19 based on interviews, but other causes of cerebral hemorrhage could not be  
20 completely ruled out. The risk of vascular injury was determined based on the  
21 diagnostic criteria at the time of examination and the participant's medical history;  
22 however, we do not have sufficient information on the control status during the  
23 follow-up.

24 On the contrary, the relationship between antiplatelet drugs (APDs) and stroke risk,



1 which may act as a protective factor, was examined supplementally. Although  
2 patients with a history of stroke or myocardial infarction were excluded from the  
3 current study, 155 of 2365 participants (145 on aspirin, 9 on cilostazol, and 1 on  
4 ticlopidine) received APDs. Seven of those on APDs had a stroke, all of which  
5 were cerebral infarctions. The risk of stroke with APDs was assessed in the overall  
6 group and in a subgroup of patients with SWAMP  $\geq 3$  points, with no significant  
7 difference in either group. However, the very small number of patients taking APDs  
8 made it difficult to draw conclusions. In addition, since the SWAMP score includes  
9 microbleeds, it cannot be said that antiplatelet agents should necessarily be used  
10 in the high-score group. However, since the risk of cerebral infarction is high in the  
11 high-score group based on the results of the present validation and  
12 antihypertensive therapy alone may not prevent cerebral infarction, monotherapy  
13 with cilostazol,<sup>15)</sup> which is considered to have a low risk of cerebral hemorrhage,  
14 may possibly be effective.

15 The purpose of using this score is to screen at brain docks and as a basis for  
16 therapeutic intervention to prevent the future stroke occurrence. Brain docks,  
17 which are extensively used in Japan, typically use MRI, and this score could be  
18 used to explain the actual condition to participants and to educate them about risk  
19 management. Unlike blood pressure, it is difficult to improve asymptomatic brain  
20 lesions, but it is possible to control their progression, and this score should  
21 contribute sufficiently to participant guidance. Therefore, the results of this study  
22 may provide a basis to suggest that participants over 65 years of age with  
23 hypertension ought to undergo brain scans.

24

1 **Conclusion**

2 In this study, we proposed a more powerful stroke prediction score by combining  
3 clinical vascular risk with MRI findings. Prospective studies using the SWAMP  
4 score are needed to validate its accuracy. In addition, preventive interventions for  
5 high-risk groups based on the score may increase its usefulness.

6

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12 **Disclosures**

13 None.

14

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