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Characteristics of aged ischemic stroke patients indicative of cardioembolism

Kosuke Matsuzono[1] · Takafumi Mashiko[1] · Tadashi Ozawa[1] · Kumiko Miura[1] · Masayuki Suzuki[1] · Kohei Furuya[1] · Misato Ozawa[1] · Yuhei Anan[1] · Haruo Shimazaki[1] · Reiji Koide[1] · Ryota Tanaka[1] · Tomoaki Kameda[2] · Shigeru Fujimoto[1]

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Abstract
The treatment of ischemic stroke has recently witnessed dramatic developments. However, there are limited data on ischemic stroke characteristics in aged patients. As part of the South Tochigi Acute Ischemic Stroke Registry, we prospectively enrolled 636 consecutive acute ischemic stroke patients (within 7 days after the onset) who were ≥ 60 years of age and who were admitted to two independent institutes from April 1, 2016 to February 28, 2019. We analyzed three groups divided by age: early-aged (60–69 years), middle-aged (70–79 years), and oldest-aged (≥ 80 years). From the 636 subjects, 194 were early-aged, 215 were middle-aged, and 227 were oldest-aged. There were significant differences in the ischemic stroke subtypes in each aging group ($p < 0.01$). The proportion of cardioembolism was 22.2% in early-aged, 27.4% in middle-aged, and 41.4% in the oldest-aged patients. The proportion of patients with a modified Rankin Scale of 0–2 at 1 year after onset decreased to 42.2% in middle-aged and 17.8% in oldest-aged with cardioembolic ischemic stroke. The proportion of patients receiving anticoagulation therapy before admission was 25.6% (36.7% of atrial fibrillation [AF]) in early-aged, 39.0% (52.3% of AF) in middle-aged, and 18.1% (21.0% of AF) in oldest-aged patients ($p < 0.001$). Our study reports characteristics of clinical ischemic stroke in an aging population. The assessment of cardiogenic embolism is important for an aging population.

Keywords Aged · Ischemic stroke · Cardioembolism · Anticoagulant therapy · Gender

Highlights

- Our prospective enrollment study revealed the clinical characteristics of aged ischemic stroke patients.
- The proportion of modified Rankin Scale of 0–2 at 1 year after onset remarkably decreased in proportion to aging category in cardioembolic ischemic stroke patients.
- However, the proportion of patients receiving anticoagulation therapy before admission decreased in proportion to aging category although atrial fibrillation was present.

✉ Kosuke Matsuzono
kmatsuzono51@jichi.ac.jp

[1] Division of Neurology, Department of Medicine, Jichi Medical University, Yakushiji 3311-1, Shimotsuke, Tochigi 329-0498, Japan

[2] Department of Neurology, Shin-Oyama City Hospital, Tochigi, Japan

Introduction

Over the last three decades there have been important developments in the treatment of ischemic stroke. As an acute reperfusion therapy, intravenous recombinant tissue-type plasminogen activator (IV rt-PA) administration within 4.5 h after the onset of stroke is effective [1, 2]. Endovascular therapy following IV rt-PA can also significantly improve clinical outcomes in certain patients with acute ischemic stroke [3–6]. Furthermore, four types of direct oral anticoagulant therapy (DOAC) have been developed for prevention of cardioembolism following non-valvular atrial fibrillation (NVAF) [7–10]. However, there are limited clinical data on the characteristics of aging ischemic stroke patients.

Japan is the most aging country in the world, and clinical data on the populations are important for studying aging-related diseases, for example, the Hisayama Study [11]. Before the recent development of stroke therapies, the Japan Standard Stroke Registry Study reported the characteristics of aging ischemic stroke patients from 1999 to 2012 [12,

13]. Although this was a large and important study, there were some limitations. For example, subjects were retrospectively enrolled, not all stroke cases in hospitals were enrolled, and some biases were present in the results.

As such, we initiated the South Tochigi Acute Ischemic Stroke Registry on April 1, 2016. In this registry, two hospitals, which covered the entire medical facilities of South Tochigi, participated. All acute ischemic stroke patients within 7 days after onset were prospectively enrolled. In the present study, we performed a comprehensive analysis of the South Tochigi Acute Ischemic Stroke Registry to determine the clinical characteristics of aged ischemic stroke patients.

Methods

Subjects

A total of 636 consecutive acute ischemic stroke patients within 7 days after onset who were ≥ 60 years of age, and who were admitted to our Division of Neurology, Department of Medicine, Jichi Medical University or the Department of Neurology, Shin-Oyama City Hospital from April 1, 2016 to February 28, 2019, were prospectively enrolled. We divided the patients into early-aged (60–69 years), middle-aged (70–79 years), and oldest-aged (≥ 80 years) groups. The Ethical Committees of Jichi Medical University and Shin-Oyama City Hospital approved this study, which was exempted approval from the institutional review board based on our guidelines (approval #Rin-Dai 17-147). All patients or families gave informed consent to participate in this study.

Baseline assessment

We recorded age, gender, body length, body weight, body mass index (BMI), smoking status, drinking status, prehospital antiplatelet therapy, prehospital anticoagulant therapy, past history of stroke, and presence of hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, congestive heart failure, atrial fibrillation (AF), arteriosclerosis obliterans, chronic kidney disease, and chronic liver dysfunction. Body length, body weight, and BMI were calculated at admission. Smoking status, drinking status, and past history of stroke were obtained from each subject. Drinking status was classified into non-consumer (0 drinks/day), adequate-drinker (1 drink/day), over-drinker (2–5 drinks/day), and heavy-drinker (> 6 drinks/day), where 1 drink = 10 g of pure alcohol. Hypertension was defined as systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg, or use of antihypertensive medication. Diabetes mellitus was defined as fasting serum glucose level ≥ 126 mg/dL, hemoglobin A1c levels ≥6.5%, or use of antidiabetic medication. Hyperlipidemia was defined as fasting serum low-density lipoprotein level ≥ 140 mg/dL and/or high-density lipoprotein level < 40 mg/dL and/or triglyceride level ≥ 150 mg/dL, or use of antihyperlipidemic agents. Chronic liver dysfunction was defined as aspartate transaminase and/or alanine aminotransferase levels ≥ 3× normal values, or diagnosis of chronic liver disease.

Clinical assessment

All subjects underwent neurological examinations by neurologists. The pre-stroke modified Rankin Scale (mRS) and the National Institute of Health Stroke Scale (NIHSS) score were assessed at admission. The acute ischemic stroke subtypes were classified based on the TOAST criteria [14]. Subjects having suffered a transient ischemic attack were also included with, but separated from cerebral infarction patients [15]. All subjects were evaluated using cranial computed tomography or magnetic resonance imaging. Based on each infarct, we evaluated the distribution (mono/multiple/undecided), location (cortex/perforator/cortex + perforator/undecided), and responsible artery (right inter-carotid artery system/left inter-carotid artery system/vertebrobasilar system/multiple/undecided). Microbleeds were defined on T2*-weighted magnetic resonance imaging as rounded areas of signal loss, 2–10 mm in diameter. Patients evaluated using only brain computed tomography were classified into an undecided group according to microbleeds. We recorded the type of acute reperfusion therapy (i.e., IV rt-PA or endovascular therapy). At discharge, neurologists evaluated stroke recurrence, mortality rate, NIHSS score, mRS, antiplatelet therapy performance, and anticoagulant therapy performance. We also surveyed the mRS at 1 year after stroke onset from 455 subjects (71.5% of total enrolled).

Data analysis

All statistical analyses were performed using statistical software (JMP 14; SAS Institute Inc., Cary, NC, USA). The baseline and clinical data of the three groups are expressed as mean ± standard error of the mean. Data were analyzed by the chi-square test, Kruskal–Wallis test, or two-way analysis of variance, as appropriate. A p value < 0.05 was considered statistically significant.

Results

From a total of 636 subjects, 194 were early-aged (60s), 215 were middle-aged (70s), and 227 were oldest-aged (≥ 80 years). The backgrounds of these groups of patients are shown in Table 1. There was a significant difference in the gender proportion between the groups, with the proportion of males decreasing from early-aged to oldest-aged

Table 1 Background of each aging group

	Early-aged (60s)	Middle-aged (70s)	Oldest-aged (≥ 80)	*p* value
n	194	215	227	
Gender				
Male	78.9%	67.0%	41.4%	< 0.001***
Female	21.1%	33.0%	58.6%	
Body length (cm, median)	164.1	160.0	150.0	< 0.001***
Body weight (kg, median)	62.7	58.1	49.4	< 0.001***
BMI (median)	23.7	23.1	21.8	< 0.001***
Smoking				
Non-smoker	28.4%	47.9%	67.4%	< 0.001***
Past-smoker	36.1%	38.6%	24.7%	
Current-smoker	34.5%	11.2%	7.1%	
Unknown	1.0%	2.3%	0.9%	
Brinkman index (median)	495	0	0	< 0.001***
Drinking				
Non-consumer	47.7%	49.5%	71.9%	< 0.001***
Adequate-drinker	24.4%	27.6%	17.6%	
Over-drinker	24.9%	16.8%	7.5%	
Heavy-drinker	2.6%	2.8%	0.9%	
Unknown	0.5%	3.3%	2.2%	
Past history and concomitant diseases				
Ischemic stroke (+)	23.7%	25.6%	25.6%	0.88
Hemorrhage stroke (+)	5.1%	6.9%	3.5%	0.27
Hypertension (+)	74.7%	78.1%	78.0%	0.66
Diabetes mellitus (+)	38.7%	32.6%	25.1%	< 0.05*
Hyperlipidemia (+)	45.9%	46.1%	33.0%	< 0.01**
CAD (+)	12.4%	16.7%	16.3%	0.40
CHD (+)	11.3%	9.3%	15.9%	0.13
NVAF				
Paroxysmal	10.3%	8.8%	12.8%	0.40
Continuous	12.4%	15.8%	26.9%	< 0.001***
Valvular AF	0.0%	1.9%	0.9%	0.15
AF	22.7%	26.5%	40.5%	< 0.001***
AO (+)	5.7%	4.2%	5.3%	0.77
CKD (+)	18.0%	18.1%	25.1%	0.12
CLD (+)	5.2%	7.4%	5.3%	0.55
Prehospital antiplatelet therapy (+)	24.2%	31.2%	32.6%	0.14
Prehospital anticoagulant therapy (+)	11.9%	16.7%	11.0%	0.17

AF Atrial fibrillation, *AO* Arteriosclerosis obliterans, *CAD* Coronary artery disease, *CHF* Congestive heart failure, *CKD* Chronic kidney disease, *CLD* Chronic liver dysfunction, *NVAF* Non-valvular atrial fibrillation

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

patients, while the proportion of females increased. Body length, body weight, BMI, smoking rate, Brinkman index, and drinking rate significantly decreased from early-aged to oldest-aged patients. As a past history, the proportion of diabetes mellitus or hyperlipidemia was significantly highest in the early-aged group, while the proportions of continuous NVAF and total AF were significantly highest in the oldest-aged group. By contrast, past ischemic history of hemorrhage stroke, hypertension, coronary artery disease, chronic heart disease, arteriosclerosis obliterans, chronic kidney disease, or chronic liver dysfunction were not significantly different between the three groups. Similarly, there were no differences in the proportions of prehospital antiplatelet or anticoagulant therapy usage among three groups.

The acute ischemic stroke data of each aging group are shown in Table 2. Both the pre-stroke mRS and NIHSS score

Table 2 Acute ischemic stroke data of each aging group

	Early-aged (60s)	Middle-aged (70s)	Oldest-aged (≥ 80)	*p* value
n	194	215	227	
Pre-stroke mRS (median)	0	0	1	< 0.001***
NIHSS score at admission (median)	3	4	5	< 0.001***
Infarct distribution				
Mono infarction	57.7%	52.6%	51.1%	0.35
Multiple infarctions	31.4%	34.4%	39.7%	
Undecided	10.8%	13.0%	9.3%	
Infarct location				
Cortex	28.9%	32.1%	42.3%	< 0.01**
Perforator	47.4%	38.1%	28.2%	
Cortex + perforator	12.4%	16.7%	20.3%	
Undecided	11.3%	13.0%	9.3%	
Infarct vascular system				
rt IC artery	27.3%	24.2%	30.4%	0.43
lt IC artery	27.8%	33.0%	29.5%	
Vertebrobasilar	27.3%	21.4%	20.3%	
Multiple	7.2%	8.4%	10.6%	
Undecided	10.3%	13.0%	9.3%	
Microbleeds				
(−)	65.0%	58.1%	63.9%	0.58
(+)	26.8%	30.2%	27.3%	
Undecided	8.3%	11.6%	8.8%	
Intravenous rt-PA therapy (+)	14.4%	9.3%	6.6%	< 0.05*
Endovascular therapy (+)	4.1%	4.2%	4.4%	0.99
Total acute reperfusion therapy (+)	18.0%	12.6%	9.7%	< 0.05*
Stroke recurrence	5.2%	3.7%	10.6%	< 0.05*
Mortality	1.6%	5.6%	4.0%	0.10
NIHSS score at discharge (median)	1	2	3	< 0.001***
mRS at discharge (median)	2	2	3	< 0.001***
mRS 1 year after stroke onset ($n = 455$, median)	1 ($n = 143$)	2 ($n = 165$)	4 ($n = 147$)	< 0.001***
Antiplatelet therapy at discharge (+)	61.3%	55.8%	49.3%	< 0.05*
Anticoagulant therapy at discharge (+)	37.1%	38.1%	45.8%	0.13

IC Internal carotid, *NIHSS* National Institute of Health Stroke Scale, *mRS* modified Rankin Scale, *rt-PA* recombinant tissue-type plasminogen activator

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

at admission were significantly highest in the oldest-aged group and lowest in the early-aged group ($p < 0.001$). Based on the infarction location, the proportion of cortical involvement was significantly highest in the oldest-aged group and lowest in the early-aged groups ($p < 0.001$), but there were no significant differences in infarction distribution, infarct artery, or microbleeds.

There were significant differences in the ischemic stroke subtypes for each aging group ($p < 0.01$; Fig. 1a, upper). The proportion of cardioembolism was 22.2% in the early-aged group, 27.4% in the middle-aged group, and 41.4% in the oldest-aged group. NIHSS scores were significantly highest in the oldest-aged group and lowest in the early-aged group at admission, day 3, day 7, and at discharge ($p < 0.001$; Fig. 1a, middle). The mean NIHSS score at admission was 5.8 ± 0.5 for early-aged, 7.8 ± 0.6 for middle-aged, and 10.0 ± 0.7 for oldest-aged patients. At discharge, the scores changed to 3.2 ± 0.4, 5.1 ± 0.6, and 7.1 ± 0.7, respectively. Based on mRS (Fig. 1a, bottom), the proportion of mRS of 0–2 changed from 90.8% (pre-hospital) to 62.4% (at discharge) to 70.7% (1 year after onset) in the early-aged group, from 85.6% (pre-hospital) to 52.1% (at discharge) to 58.3% (1 year after onset) in the middle-aged group, and from 68.6% (pre-hospital) to 42.7% (at discharge) to 32.0% (1 year after onset) in the oldest-aged group. Note that the proportion of mRS of 0–2 changed in a J-shape from pre-hospital

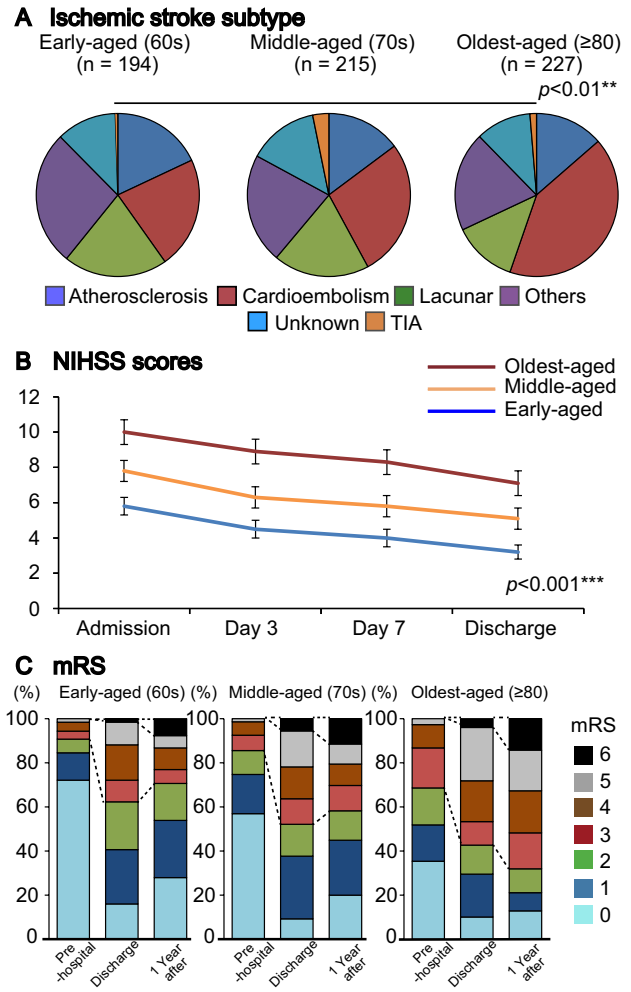

Fig. 1 Ischemic stroke characteristics of each early-aged, middle-aged, or oldest-aged aging groups. **a** The ischemic stroke subtypes of each aging group. **b** National Institute of Health Stroke Scale (NIHSS) scores at admission, day 3, day 7, and at discharge in each aging group. **c** Proportions of the modified Rankin Scale (mRS) before admission, at discharge, and 1 year after onset in each aging group

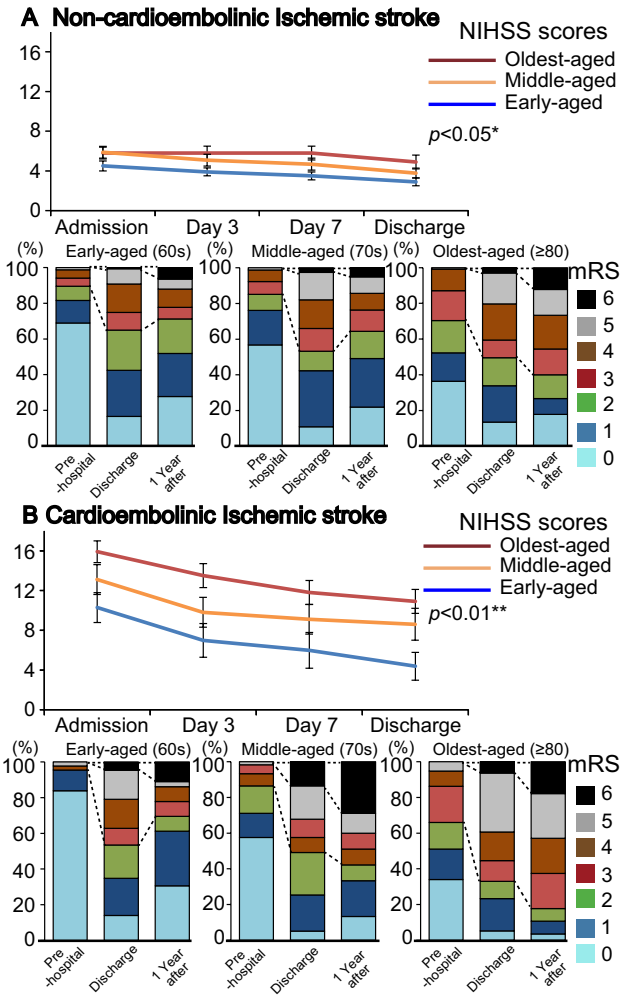

Fig. 2 Separate characteristics of non-cardioembolic and cardioembolic ischemic stroke patients. **a** NIHSS scores and proportions of mRS in each aging group in non-cardioembolic ischemic stroke patients. **b** NIHSS scores and proportions of mRS in each aging group in cardioembolic ischemic stroke patients

to 1 year after onset in both the early-aged and middle-aged subjects, while that for the oldest-aged group decreased continuously. By contrast, the proportion of mRS of 6 (death) increased to 1.6% (at discharge) and 7.7% (1 year after onset) in the early-aged group, to 5.6% (at discharge) and 11.5% (1 year after onset) in the middle-aged group, and to 4.0% (at discharge) and 14.3% (1 year after onset) in the oldest-aged group. The mean mRS at discharge and 1 year after stroke onset were significantly different between the three groups, and were highest in oldest-aged patients and lowest in early-aged patients (Table 2).

We also analyzed the NIHSS scores and mRS of non-cardioembolic ischemic stroke and cardioembolic ischemic stroke patients separately (Fig. 2). Even for non-cardioembolic ischemic stroke, the NIHSS scores were significantly different between the three groups through at admission, day 3, day 7, and at discharge ($p < 0.05$; Fig. 2a, upper). The mean NIHSS score at admission was 4.5 ± 0.5 in the early-aged group, 5.9 ± 0.6 in the middle-aged group, and 5.8 ± 0.6 in the oldest-aged group. The scores at discharge changed to 2.9 ± 0.4, 3.8 ± 0.5, and 4.9 ± 0.7, respectively. The proportion of mRS of 0–2 in non-cardioembolic ischemic stroke patients changed from 89.5% (pre-hospital) to 64.9% (at discharge) to 71.3% (1 year after onset) in the early-aged group, from 85.2% (pre-hospital) to 53.2% (at discharge) to 64.4% (1 year after onset) in the middle-aged group, and from 70.5% (pre-hospital) to 49.6% (at discharge) to 40.0% (1 year after onset) in the oldest-aged group (Fig. 2a, bottom). By contrast, the proportion of mRS of 6 increased to 0.7% (at discharge) and 6.5% (1 year after onset) in the early-aged group, to 2.6% (at discharge) and 5.1% (1 year after onset) in

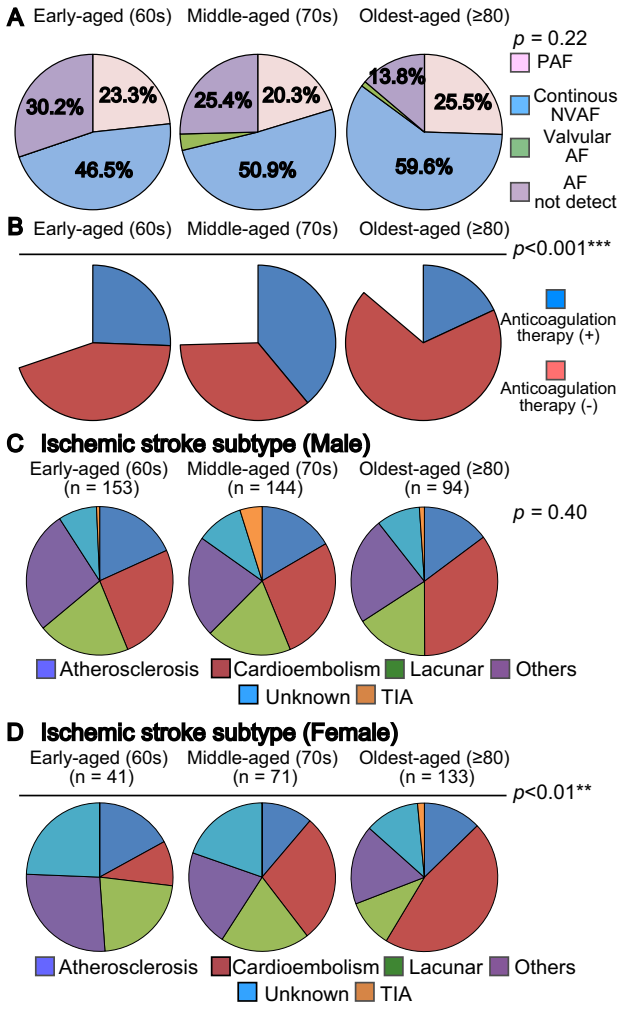

Fig. 3 Atrial fibrillation (AF) data of cardioembolic ischemic stroke patients and the differences in the ischemic stroke subtypes separated by gender for each aging group. **a** Proportion of AF in each aging group in cardioembolic ischemic stroke patients. The proportions of PAF, CAF, VAF, and undetected AF are also shown. **b** Description of whether anticoagulation therapy (+) was received, or not (−), before admission in each aging group. The proportion of anticoagulation therapy (+) before admission was 25.6% in early-aged (36.7% of AF detected), 39.0% (52.3%) in middle-aged, and 18.1% (21.0%) in oldest-aged ($p<0.001$) cardioembolic ischemic stroke patients. **c** Male ischemic stroke subtypes for each aging group. **d** Female ischemic stroke subtypes for each aging group

the middle-aged group, and to 3.0% (at discharge) and 12.2% (1 year after onset) in the oldest-aged group.

For cardioembolic ischemic stroke, the NIHSS scores were significantly different between the three groups at admission, day 3, day 7, and at discharge ($p<0.01$; Fig. 2b, upper). The mean NIHSS score at admission was 10.3 ± 1.5 in the early-aged group, 13.1 ± 1.5 in the middle-aged group, and 15.9 ± 1.1 in the oldest-aged group. At discharge, the scores changed to 4.4 ± 1.4, 8.6 ± 1.6, and 10.9 ± 1.2, respectively. The proportion of mRS of 0–2 for cardioembolic ischemic stroke changed from 95.3% (pre-hospital) to 53.5% (at discharge) to 69.5% (1 year after onset) in the early-aged group, from 86.5% (pre-hospital) to 49.1% (at discharge) to 42.2% (1 year after onset) in the middle-aged groups, and from 65.9% (pre-hospital) to 33.0% (at discharge) to 17.8% (1 year after onset) in the oldest-aged group (Fig. 2b, bottom). By contrast, the proportion of mRS of 6 increased to 4.7% (at discharge) and 11.1% (1 year after onset) in the early-aged group, to 13.6% (at discharge) and 28.9% (1 year after onset) in the middle-aged group, and to 6.4% (at discharge) and 17.9% (1 year after onset) in the oldest-aged group. The proportion of mRS of 0–2 changed to a J-shape from the pre-hospital stage to 1 year after onset in early-aged and middle-aged non-cardioembolic ischemic stroke patients and in early-aged cardioembolic ischemic stroke patients, but decreased continuously in oldest-aged non-cardioembolic ischemic stroke patients and in middle-aged and oldest-aged cardioembolic ischemic stroke patients.

Next we examined AF in the cardioembolic ischemic stroke patients (Fig. 3a, b). From a total 636 ischemic stroke subjects, 196 subjects (30.8%) were diagnosed as cardioembolic stroke, of whom 155 subjects (79.1%) exhibited AF before admission. Based on the cardioembolic ischemic stroke subtypes, in early-aged patients, 23.3% were paroxysmal AF (PAF), 46.5% were continuous AF (CAF), 0% were valvular AF (VAF), and 30.2% were not AF. By contrast, in middle-aged patients, 20.3% were PAF, 50.9% were CAF, 3.4% were VAF, and 25.4% were not AF, while in oldest-aged patients, 25.5% were PAF, 59.6% were CAF, 1.1% were VAF, and 13.8% were not AF (Fig. 3a). In cardioembolic ischemic stroke patients, the proportion of NVAF was 69.8% in early-aged, 71.2% in middle-aged, and 85.1% in oldest-aged patients ($p=0.22$), while the proportion of patients receiving anticoagulation therapy before admission was 25.6% (36.7% of AF), 39.0% (52.3% of AF), and 18.1% (21.0% of AF) ($p<0.001$; Fig. 3b), respectively.

Finally, we analyzed the differences in the ischemic stroke subtypes based on gender for each aging group (Fig. 3c, d). In male ischemic stroke subtypes, there was no difference for each aging group ($p=0.40$; Fig. 3c). However, there were significant differences in the female ischemic stroke subtypes for each aging group ($p<0.01$; Fig. 3d) and the proportion of cardioembolism was 9.8% in early-aged, 28.2% in middle-aged, and 45.9% in the oldest-aged patients.

Discussion

Our present study shows that the proportion of cardioembolinic ischemic stroke subtypes increased from early-aged to oldest-aged patients. We speculate that the major reason is that the prevalence of AF increases in proportion to aging

[16]. Our study also supports the importance of AF treatment in a recently aging society. In addition, we also speculate that gender differences may be linked with an increase proportion of cardioembolism in the oldest-aged patients. The proportion of cardioembolism subtype increased from early-aged to oldest-aged patients among females but not among males. This result corresponds to the findings of a previous report [17] and suggest the importance of considering gender differences because the proportion of females became large when age was ≥80.

Our study also showed a low proportion of patients receiving anticoagulation therapy in all three groups, particularly in the oldest-aged group, although AF was detected after admission. Even if cardioembolic ischemic stroke occurred once, the proportion of mRS of 0–2 at 1 year after onset decreased to 42.2% in the middle-aged group, and to only 17.8% in the oldest-aged group. The use of anticoagulation therapy is important to avoid or reduce the degree of cardioembolism [18, 19]. We suggest that there are two major factors underlying our findings. First, some cryptogenic stroke occurred by AF. In our study, the proportion of cardioembolic ischemic stroke patients with no AF before admission was 30.2% in early-aged patients and 25.4% in middle-aged patients. In the CYRSTAL AF study, an AF episode was detected in 29 of 221 cryptogenic stroke patients within 12 months, and in 42 patients after 36 months [20]. In some cryptogenic stroke cases, a number of monitoring methods, including insertable cardiac monitors, were reported to be effective for detecting AF [21–23]. In addition, some AF were detected by medical check-ups [24]. Our South Tochigi Acute Ischemic Stroke Registry supports the importance of detecting AF. Second, we speculate that some cases of AF did not receive anticoagulation therapy, despite the detection of AF, because the proportion of continuous NVAF, which is easy to detect, increased in the oldest-aged patients. These findings may also be related to the increase in pre-hospital mRS (Fig. 2b). However, the induction of anticoagulant therapy likely depends on the $CHADS_2$ score rather than on mRS [25, 26].

The Stroke and Cardiovascular Disease Control Act was approved in Japan in December 2018 [27], which purpose is to establish comprehensive nationwide approaches for prevention, treatment, and patient support. Our present study provides new clinical data important for achieving this goal. A limitation of our study is the small number of stroke centers and the lack of multi-facilities. Furthermore, only Japanese patients were enrolled, and the findings cannot be applied to other cultural groups. Finally, complete removal of confounding factors, which may have affected our findings, is difficult.

Conclusion

Our study examined the clinical characteristics of ischemic stroke data from an aging population in Japan, for which an assessment of cardiogenic embolism is important.

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Author contributions KosukeM calculated the results and drafted the manuscript. KosukeM, TM, TO, KumikoM, MS, KF, MO, and TM collected the data. HS, RK, and RT helped draft the manuscript. SF conceived the study, participated in its coordination, and helped draft the manuscript. All authors read and approved the final manuscript.

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Data availability All data and materials used in this work are available based on reasonable request to the corresponding author.

Compliance with ethical standards

Conflict of interest Ryota Tanaka received honoraria (lecture fees) from Daiichi Sankyo Co., Ltd., Nippon Boehringer Ingelheim, Co., Ltd., Pfizer Inc., Bristol Myers Squibb, and Bayer Yakuhin Ltd. Shigeru Fujimoto received honoraria (lecture fees) from Daiichi Sankyo Co., Ltd., Nippon Boehringer Ingelheim, Co., Ltd., Pfizer Inc., Bristol Myers Squibb, and Bayer Yakuhin Ltd.

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