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CLINICAL ARTICLE

Detection rates and sites of unruptured intracranial aneurysms according to sex and age: an analysis of MR angiography–based brain examinations of 4070 healthy Japanese adults

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OBJECTIVE The purpose of this study was to evaluate the detection rate and occurrence site according to patient sex and age of unruptured intracranial aneurysms detected through MRI and MR angiography (MRA).

METHODS A total of 4070 healthy adults 22 years or older (mean age [± SD] 50.6 ± 11.0 years; 41.9% women) who underwent a brain examination known as "Brain Dock" in the central Tokyo area between April 2014 and March 2015 were checked for unruptured saccular aneurysm using 3-T MRI/MRA. The following types of cases were excluded: 1) protrusions with a maximum diameter < 2 mm at locations other than arterial bifurcations, 2) conical protrusions at arterial bifurcations with a diameter < 3 mm, and 3) cases of suspected aneurysms with unclear imaging of the involved artery. When an aneurysm was definitively diagnosed, the case was included in the aneurysm group. The authors also investigated the relationship between aneurysm occurrence and risk factors (age, sex, smoking history, hypertension, diabetes, and hyperlipidemia).

RESULTS One hundred eighty-eight aneurysms were identified in 176 individuals (detection rate 4.32%), with the detection rate for women being significantly higher (6.2% vs 3.0%, $p < 0.001$). The average age in the aneurysm group was significantly higher than in the patients in whom aneurysms were not detected (53.0 ± 11.1 vs 50.5 ± 11.0 years). The detection rate tended to increase with age. The detection rates were 3.6% for people in their 30s, 3.5% for those in their 40s, 4.1% for those in their 50s, 6.9% for those in their 60s, and 6.8% for those in their 70s. Excluding persons in their 20s and 80s—age groups in which no aneurysms were discovered—the detection rate in women was higher in all age ranges. Of the individuals with aneurysms, 12 (6.81%) had multiple cerebral aneurysms; no sex difference was observed with respect to the prevalence of multiple aneurysms. Regarding aneurysm size, 2.0–2.9 mm was the most common size range, with 87 occurrences (46.3%), followed by 3.0–3.9 mm (67 [35.6%]) and 4.0–4.9 mm (20 [10.6%]). The largest aneurysm was 13 mm. Regarding location, the internal carotid artery (ICA) was the most common aneurysm site, with 148 (78.7%) occurrences. Within the ICA, C_1 was the site of 46 aneurysms (24.5%); C_2, 57 (30.3%); and C_3, 29 (15.4%). The aneurysm detection rates for C_2, C_3, and C_4 were 2.23%, 1.23%, and 0.64%, respectively, for women and 0.68%, 0.34%, and 0.21%, respectively, for men; ICA aneurysms were significantly more common in women than in men (5.27% vs 2.20%, $p < 0.001$). Multivariate logistic regression analysis revealed that age ($p < 0.001$, OR 1.03, 95% CI 1.01–1.04), female sex ($p < 0.001$, OR 2.28, 95% CI 1.64–3.16), and smoking history ($p = 0.011$, OR 1.52, 95% CI 1.10–2.11) were significant risk factors for aneurysm occurrence

CONCLUSIONS In this study, both female sex and older age were independently associated with an increased aneurysm detection rate. Aneurysms were most common in the ICA, and the frequency of aneurysms in ICA sites was markedly higher in women.

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KEYWORDS cerebral aneurysm; MRA; brain check; vascular disorders

ABBREVIATIONS ACA = anterior cerebral artery; ACoA = anterior communicating artery; ICA = internal carotid artery; MCA = middle cerebral artery; MIP = maximum intensity projection; MRA = MR angiography; PCoA = posterior communicating artery; PICA = posterior inferior cerebellar artery; VA = vertebral artery.

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In Japan, which has the highest prevalence of MRI equipment in the world, the number of facilities incorporating brain examinations into medical care is increasing. Brain assessments were established in Japan for the first time in 1988. MRI and MR angiography (MRA) are the core examinations conducted during a checkup and play an important role in screening for unruptured intracranial aneurysms. The 2012 report of UCAS Japan[9] (the Unruptured Cerebral Aneurysm Study of Japan) shows the yearly rupture rate by size and location for aneurysms ≥ 3 mm. With this report as a reference, treatment strategies for detected unruptured aneurysms are currently being studied, but standard data based only on MRA that could provide an index for the detection frequency of unruptured intracranial aneurysms are almost nonexistent.

We performed a large-scale study of individuals who underwent brain imaging examinations in central Tokyo, evaluating their 3-T MRI and MRA findings in detail and calculating aneurysm detection rates. In line with the role of brain examinations, the examinees are informed of the possibility of an aneurysm even when the findings are not definitive and such a lesion is only suspected. For this study, confirmed aneurysm cases were extracted and analyzed, while suspected cases were excluded.

Methods

Study Group

A total of 4084 healthy adults, essentially without symptoms, underwent a standardized brain evaluation known as "Brain Dock" between April 2014 and March 2015 at the Tokyo Midtown Clinic. Fourteen individuals with a history of brain surgery were excluded, and findings in the remaining 4070 individuals (age range 22–89 years) were considered for inclusion in this analysis (Fig. 1). MRA examination for unruptured intracranial aneurysm was performed using Magnetom Spectra 3-T MRI (Siemens Inc.). At that time, T1-weighted, T2-weighted, FLAIR, and diffusion-weighted imaging sequences were simultaneously recorded and used to assist in the diagnosis. Additionally, when a brain aneurysm was suspected based on the MRA maximum intensity projection (MIP) images, the images were carefully evaluated via primary interpretation by a radiologist and secondary interpretation by a neurosurgeon with more than 17 years' experience. The secondary interpretation results were reported to the examinees, and the detection rate was calculated, including suspicious cases based on these results. All images from these aneurysm cases were assessed a second time. We excluded cases in which a protrusion area < 2 mm outside of an arterial bifurcation was found, or the area corresponding to arterial bifurcation protruded in a conical shape < 3 mm in diameter, or the image of the branched artery was unclear. Individuals with confirmed aneurysms were included in the aneurysm group. This group was evaluated for sex, age range, aneurysm occurrence site frequency and detection rate, and aneurysm size. Suspicious cases in which an aneurysm could not be completely excluded and cases in which an aneurysm was excluded were combined into a nonverified aneurysm group. We also investigated the relationship between aneurysm occurrence and risk factors (age, sex, smoking history, hypertension [blood pressure > 140/90 mm Hg], diabetes [HbA1c > 6.5%], and hyperlipidemia [LDL > 180 mg/dl]). The study protocol was consistent with the Japanese Government's Ethical Guidelines Regarding Epidemiological Studies in accordance with the Declaration of Helsinki. Informed consent was waived because of minimal patient risk and because only de-identified data were included.

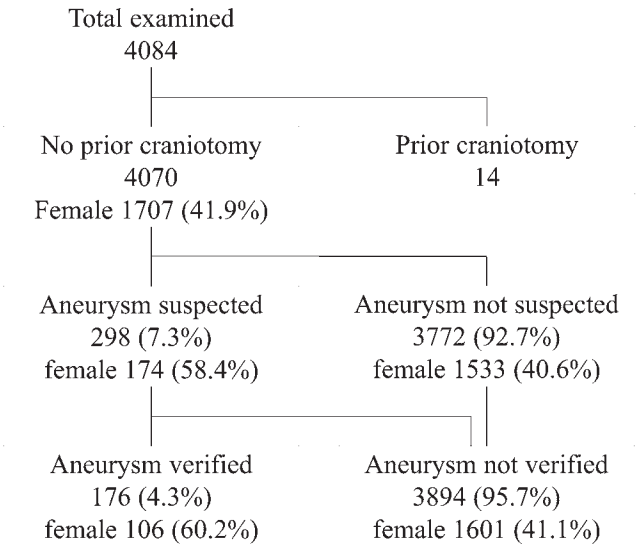

FIG. 1. Flowchart for this study. The values are numbers of examinees and percentages.

Statistical Analysis

The aneurysm detection rate was calculated for each age range and for each sex. Thereafter, the aneurysm detection rates according to sex for each age range were compared using the chi-square test. In addition, the detection rate was calculated based on the site of the detected aneurysms. A p value < 0.05 was considered statistically significant. Furthermore, the multivariate analysis of risk factors for aneurysm occurrence, such as age, sex, smoking history, hypertension, diabetes, and hyperlipidemia, was performed using the logistic regression technique. All statistical analyses were performed with Excel 2013 (Microsoft Corp.) and R 3.0.2 (available at http://www.r-project.org).

Results

Of the 4070 participants, 1707 (41.9%) were female (mean age [± SD] 51.4 ± 11.7 years) and 2363 (58.1%) were male (mean age 50.0 ± 10.4 years). The female/male ratio was 0.72:1. The mean age was significantly higher for women ($p < 0.05$). The verified aneurysm group, in which aneurysms were diagnosed with certainty, consisted of 176 individuals (detection rate 4.32%) and 188 aneurysms (Fig. 1). Suspicious cases, in which aneurysms could not be completely excluded, comprised 122 individuals (3.00%) and 130 aneurysms.

Of the 176 members of the verified aneurysm group,

TABLE 1. Baseline characteristics of 4070 screened individuals stratified by the presence of verified aneurysms

Characteristic	Total (n = 4070)	Verified Aneurysms (n = 176)	No Verified Aneurysms (n = 3894)	p Value
Female sex	1707 (41.9)	106 (60.2)	1601 (41.1)	<0.005
Mean age in yrs	50.6 ± 11.0	53.0 ± 11.1	50.5 ± 11.0	<0.001
Medical history				
Hypertension	586 (14.4)	24 (13.6)	562 (14.4)	0.769
Diabetes mellitus	172 (4.2)	7 (4.0)	165 (4.2)	0.981
Hyperlipidemia	501 (12.3)	23 (13.1)	478 (12.3)	0.754
Former or current smoker	1750 (43.0)	80 (45.5)	1670 (42.9)	0.518

Values are number of individuals (%) unless otherwise indicated. The p value for sex was analyzed as a single variable with the chi-square test. The p value for the mean age of the patients was calculated with the Student t-test.

106 (60.2%) were women (female/male ratio 1.51:1). In the verified aneurysm group, there were significantly more women ($p < 0.005$, Table 1). Multiple cerebral aneurysms were confirmed in 12 individuals (6.81%), and a sex difference was not found. All examinees were between the ages of 22 and 89 years (mean age 50.6 ± 11.0 years); however, the mean age of individuals in the verified aneurysm group was significantly greater than the mean age of those in the nonverified aneurysm group (53.0 ± 11.1 vs 50.5 ± 11.0 years, $p < 0.001$). No significant difference was found between the verified aneurysm and nonverified aneurysm groups regarding the presence of hypertension, diabetes, hyperlipidemia, or smoking. Table 2 shows the number of verified aneurysm and nonverified aneurysm cases according to sex and age range and the ratios.

The aneurysm detection rate increased with age and was 3.63% for the 30s, 3.53% for the 40s, 4.12% for the 50s, 6.95% for the 60s, and 6.76% for the 70s. The overall aneurysm detection rate for women was 6.2%, and it was significantly higher than the rate for men ($p < 0.001$). Even after excluding the 20s and 80s age groups, in which there were no aneurysm cases, the aneurysm detection rate was still higher for women in every age group. In particular, the rate was significantly higher for women than for men in the 40s ($p < 0.05$), 50s ($p < 0.05$), and 70s ($p < 0.01$) age groups.

The occurrence sites of the 188 aneurysms detected in the 176 individuals in the aneurysm group were the internal carotid artery (ICA), which was the most common site, with 148 (78.7%) of the detected aneurysms (right/left ratio 66:82), followed by the anterior communicating artery (ACoA) with 22 (11.7%) and the middle cerebral artery (MCA) with 17 (9.0%; right/left ratio 12:5). When the ICA was divided into the 5 segments proposed in 1938 by Fischer,[1] C_2—from the initial segment of the ophthalmic artery to the proximal side of the posterior communicating artery (PCoA)—had 57 aneurysms (30.3%; right/left ratio 22:35), the most of any section. The distal area of the ICA from the PCoA to the anterior cerebral artery (ACA)—C_1—had 46 aneurysms (24.5%; right/left ratio 23:23), and C_3—from the proximal curve of the carotid siphon to the ophthalmic artery—had 29 (15.4%; right/left ratio 9:20) (Fig. 2, Table 3). Specifically, in C_1, there were 32 aneurysms in the PCoA section, 13 in the anterior choroidal artery section, and 1 in the apex of the ICA. There were 16 (8.5%; right/left ratio 12:4) in the cavernous segment (C_4). No aneurysms were found from the inlet of the carotid artery to the proximal cavernous sinus (C_5). Moreover, only 1 aneurysm was observed in the posterior circulation, a 4.3-mm lesion in the left vertebral artery (VA) and posterior inferior cerebellar artery (PICA). More aneurysms tended to occur on the right in the MCA and C_4 and on the left in C_3.

Smaller aneurysms tended to be more common. Of the 188, 87 (46.3%) were 2–2.9 mm; 67 (35.6%), 3–3.9 mm; 20 (10.6%), 4–4.9 mm; 9 (4.8%), 5–5.9 mm; and 5 (2.7%), ≥ 6 mm. A total of 101 (53.7%) of the aneurysms were ≥ 3 mm; aneurysms ≥ 3 mm were identified in 97 individuals (detection rate 2.38%) (Table 3).

Comparison of detection rates according to sex for each occurrence site showed a statistically significant difference between the rates for men and women with respect to the ICA as the occurrence site (5.27% for women and 2.20% for men [female/male ratio 2.40:1], $p < 0.001$), but no significant difference with respect to either ACoA or MCA (ACoA, 0.64% for women and 0.47% for men [female/

TABLE 2. Age distribution of the patients with verified aneurysms

Age Group (yrs)	Total (%)		Women (%)		Men (%)		
	Verified Aneurysms	No Verified Aneurysms	Verified Aneurysms	No Verified Aneurysms	Verified Aneurysms	No Verified Aneurysms	p Value
20–29	0 (0)	52 (100)	0 (0)	32 (100)	0 (0)	20 (100)	
30–39	21 (3.6)	558 (96.4)	12 (5.8)	194 (94.2)	9 (2.4)	364 (97.6)	0.06
40–49	49 (3.5)	1338 (96.5)	28 (5.0)	535 (95.0)	21 (2.5)	803 (97.5)	<0.05
50–59	50 (4.1)	1164 (95.9)	27 (5.6)	457 (94.4)	23 (3.2)	707 (96.8)	<0.05
60–69	41 (6.9)	549 (93.1)	25 (8.9)	256 (91.1)	16 (5.2)	293 (94.8)	0.08
70–79	15 (6.8)	207 (93.2)	14 (11.1)	112 (88.9)	1 (1.0)	95 (99.0)	<0.01
80–89	0 (0)	26 (100)	0 (0)	15 (100)	0 (0)	11 (100)	
All	176 (4.3)	3894 (95.7)	106 (6.2)	1601 (93.8)	70 (3.0)	2293 (97.0)	<0.001

The p value for sex was analyzed as a single variable with the chi-square test.

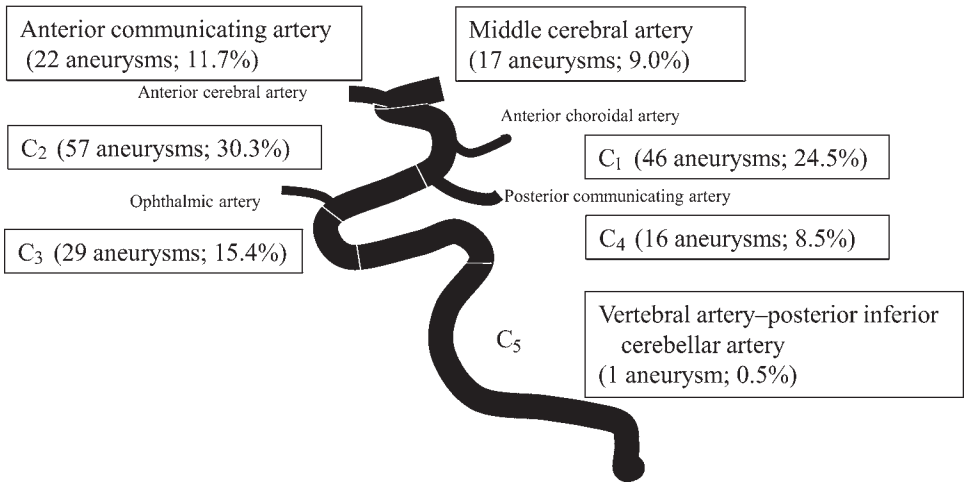

FIG. 2. Sites of 188 verified aneurysms.

male ratio 1.36:1]; MCA, 0.47% for women and 0.34% for men [female/male ratio 1.38:1]). Regarding ICA segments, no significant difference was found between the rates for men and women in C_1. However, in C_2 the rate was 2.23% for women and 0.68% for men (female/male ratio 3.28:1, $p < 0.001$); in C_3 the rate was 1.23% for women and 0.34% for men (female/male ratio 3.62:1, $p < 0.005$); and in C_4 it was 0.64% for women and 0.21% for men (female/male ratio 3.05:1, $p = 0.05$). In C_2 and C_3, the detection rate for women was significantly higher (Table 4).

The multivariate logistic regression analysis revealed that age ($p < 0.001$, OR 1.03, 95% CI 1.01–1.04), female sex ($p < 0.001$, OR 2.28, 95% CI 1.64–3.16), and smoking history ($p = 0.011$, OR 1.52, 95% CI 1.10–2.11) were significant risk factors for aneurysm occurrence (Table 5).

Discussion

Intracranial Aneurysm Detection Rate

To date, there have been a handful of studies on the detection rate of unruptured intracranial aneurysms; however, there are few reports on healthy adults who underwent brain examinations. Regarding the diagnosis of intracranial aneurysm using 1.5-T MRA, Jeon et al.[5] reported that intracranial aneurysms were detected in 137 (4.5%) of 3049 outpatient examinees. In that report, aneurysms ≥ 2 mm were investigated and 15% of aneurysms were < 3 mm. Additionally, in a 1994 study by Nakagawa and Hashi,[8] in which MRI was conducted on 400 healthy adult volunteers and digital subtraction angiography was conducted on 370 of these volunteers, intracranial aneurysms were detected in 6.5% of the participants; 59.3% of the detected aneurysms were ≤ 5 mm, but the minimum diameter was not clearly stated. In our present study, 87 (46.3%) of the 188 aneurysms detected were < 3 mm. Although a clear diagnosis was difficult with sizes < 2 mm, it is thought that 3-T MRI/MRA increases the ability to diagnose aneurysms of 2–3 mm.

In 1990, Inagawa and Hirano[3] reported their analysis of the results of 10,259 autopsies performed at a single facility between 1951 and 1987; intracranial aneurysms were identified in 84 individuals (102 aneurysms, detection rate of 0.82%). In their study, small aneurysms (< 4 mm) were common (54%), but the minimum diameter was not clarified. Additionally, in a study by Iwamoto et al.,[4] 73 intracranial aneurysms were found in 57 individuals (detection rate of 4.6%) through 1230 autopsies conducted in the town of Hisayama between 1962 and 1991. In that study, however, the cavernous carotid artery and carotid cave were not assessed. In the autopsy reports of Inagawa

TABLE 3. Size and site of 188 verified aneurysms

Site	2.0–2.9 mm	3.0–3.9 mm	4.0–4.9 mm	5.0–5.9 mm	≥6.0 mm	Total (%)
ACoA	13	5	2	1	1	22 (11.7)
ICA	69	55	16	5	3	148 (78.7)
C_1	16	21	5	2	2	46 (24.5)
C_2	29	17	8	2	1	57 (30.3)
C_3	13	14	2	0	0	29 (15.4)
C_4	11	3	1	1	0	16 (8.5)
MCA	5	7	1	3	1	17 (9.0)
VA/PICA	0	0	1	0	0	1 (0.5)
Total (%)	87 (46.3)	67 (35.6)	20 (10.6)	9 (4.8)	5 (2.7)	188

TABLE 4. Detection of verified aneurysms stratified by site and sex

Site	Women (n = 1707)	Men (n = 2363)	Total (n = 4070)
ACoA	11 (0.64)	11 (0.47)	22 (0.54)
ICA	90 (5.27)	52 (2.20)	142 (3.49)
C_1	20 (1.17)	23 (0.97)	43 (1.06)
C_2	38 (2.23)	16 (0.68)	54 (1.33)
C_3	21 (1.23)	8 (0.34)	29 (0.71)
C_4	11 (0.64)	5 (0.21)	16 (0.39)
MCA	8 (0.47)	8 (0.34)	16 (0.39)
VA/PICA	0 (0)	1 (0.04)	1 (0.03)

Data represent the number of individuals (%) in whom 1 or more aneurysms were detected on the specified artery or segment. The percentage value is the detection rate.

et al., the extent of evaluation of the central area of the ICA was not specified.

Sex Differences

In the present study, there were fewer female than male examinees, but the aneurysm detection rate tended to be higher in women for every age group (Table 2). A report by UCAS Japan[9] stated that the aneurysm detection rate in women is approximately twice that in men. In our present results, the findings were similar, with men having a 3.0% detection rate compared with 6.2% in women. To the best of our knowledge, no reports investigating the sex difference at each occurrence site exist. In this study, the detection rates were calculated by occurrence site and also by sex, and in all areas of the anterior circulation, the rate tended to be higher in women. Regarding the central area of the ICA (C_2 and C_3), there was a marked sex difference, with the rate in women being significantly higher than that in men. Considering the ICA as a whole, women had significantly higher rates than men (Table 4).

Jeon et al.[5] reported that there was no sex difference in detection rate and that the rate increased with age for both sexes, with an overall value of about 5%. In the present study, excluding the 20s and 80s age groups, the female detection rate was higher across all age ranges.

Site and Diagnosis

To date, there have been multiple reports on ruptured intracranial aneurysm occurrence sites, the most common site being the ACoA at 26%–34%.[2,6,7] However, there are a few reports regarding occurrence site for unruptured intracranial aneurysms. In one study regarding unruptured intracranial aneurysms detected during autopsy, the most common occurrence site was the MCA, which was the site of 39 (38%) of 102 intracranial aneurysms.[3] The MCA was the most common site in another report also, in which 23 (32%) of 72 intracranial aneurysms were located.[4] In these reports, since the search site was limited to the dura mater during autopsy, it can be presumed that the assessment of the ICA, and in particular, the assessment of the central area from the anterior clinoid process, was insufficient, and that the frequency of ICA aneurysms was not only 29 (28%) and 8 (11%), respectively. A study similar to the present one revealed the ICA as the most common occurrence site (86 [52%] of 164 aneurysms detected by MRA).[4] However, in our current research, by examining a more central area, our ICA aneurysm occurrence of 148 (78.7% of detected aneurysms) showed a higher rate than previous studies. When the findings are limited to the distal ICA (C_1 and C_2), our detection rate of 103 (54.8%) of 188 aneurysms is similar to the rates reported in these other studies.

TABLE 5. Multivariate logistic regression analysis of risk factors for aneurysm occurrence

Risk Factor	OR (95% CI)	p Value
Age	1.03 (1.02–1.01)	<0.001
Female sex	2.28 (1.64–3.17)	0.001
Smoking history	1.52 (1.10–2.11)	0.011
Hypertension	0.78 (0.48–1.26)	0.31
Diabetes	0.62 (0.31–1.27)	0.19
Hyperlipidemia	0.89 (0.61–1.29)	0.52

Limitations

Unfortunately, there are limitations of the generalizability of the results in this study due to the ethnic homogeneity of the Japanese study population and the lack of information about family history. Although the large number of examinees (4070) and the use of 3-T MRI/MRA revealed a higher incidence of unruptured aneurysms than previously reported, further studies with a consideration of other factors will be needed to address this issue more completely.

Conclusions

In 4070 healthy adults who underwent brain evaluation, there were 176 individuals with confirmed intracranial aneurysm (188 aneurysms, detection rate 4.32%). The detection rate increased with age, and aneurysms were identified more frequently in women. Regarding aneurysm site frequency, the ICA had the most aneurysms, and the rate for women in the central area of the ICA was particularly high.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Imaizumi, Mizutani. Acquisition of data: Imaizumi, Mizutani, Shimizu, Taguchi. Analysis and interpretation of data: Imaizumi, Mizutani, Sato. Drafting the article: Imaizumi, Shimizu. Critically revising the article: Imaizumi, Mizutani, Shimizu. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Imaizumi. Statistical analysis: Imaizumi, Shimizu, Sato. Administrative/technical/material support: Imaizumi, Taguchi. Study supervision: Mizutani.

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