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Clinical characteristics of aneurysmal subarachnoid hemorrhage in the elderly over 75; would temporal muscle be a potential prognostic factor as an indicator of sarcopenia?

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ABSTRACT

Objectives: Age of patients with subarachnoid hemorrhage (SAH) is increasing. It is challenging to decide whether to perform aneurysm treatment and to predict their prognosis. We assumed that elderly patients with SAH who do not suffer from sarcopenia tend to have good outcomes. Temporal muscle thickness (TMT) and area (TMA) are useful indicators of sarcopenia. We investigated the clinical characteristics, including temporal muscle, in SAH patients over 75 years old.

Patients and methods: We retrospectively analyzed 49 SAH patients over 75 years old from 2014 to 2018, who accounted for 37% of the patients in all age group. The correlations between the clinical variables and the modified Rankin Scale (mRS) at discharge were analyzed.

Results: Of the all 49 SAH patients over 75 years old, premorbid mRS, WFNS grade, lymphocyte, aneurysm size, TMT, TMA, showed significant correlations with mRS at discharge. Men and the absence of hydrocephalus were correlated with favorable outcomes. Thirteen of the 24 patients over 75 years old whose WFNS grade were I to III but also who underwent aneurysm treatment had favorable outcomes (mRS 0–2), and their standardized TMT divided by height, by weight, and TMA divided by weight were significantly larger than that with poor outcomes.

Conclusion: Aneurysm intervention should be considered when patients over 75 years old do not suffer from sarcopenia. Temporal muscle would indicate premorbid mRS and be potentially useful to decide surgical indication and to predict outcome after aneurysm treatment in the elderly.

1. Introduction

The “advanced elderly,” defined as people over 75 years old in Japan by the Japanese Ministry of Health, Labor and Welfare, comprised 13.8% of the total Japanese population in 2017. The incidence of subarachnoid hemorrhage (SAH) has been reported to increase with age in Japan [1]. We sometimes encounter such elderly patients with SAH, but it is challenging to decide whether to perform aneurysm treatment for preventing rerupture and to predict their prognosis. This is because the prognoses and best treatment strategies for elderly patients with SAH are unclear, and the outcomes are generally poor [2,3]. However, several case series reported favorable outcomes in elderly patients with SAH who had undergone clipping surgery or coiling [4–6]. Therefore, advanced age alone does not preclude patients with aneurysmal ruptures from surgical or endovascular intervention.

Sarcopenia is defined as a loss of skeletal muscle mass, an impaired health state that is characterized by locomotive disorder, increased risk of falls and fractures, difficulty in performing activities of daily living (ADL), loss of independence, and increased risk of mortality [7]. We assumed that elderly patients with SAH who do not appear to suffer from sarcopenia (e.g., farmers, fishers) tend to have good outcomes. In this study, we tried to scientifically demonstrate this hypothesis “Spry old women and men can undergo aneurysm treatment for SAH, and the outcomes are favorable.”

This study was performed to analyze the clinical characteristics and outcomes in elderly patients with SAH over 75 years old. Besides, focusing on sarcopenia, we analyzed the relationship between temporal muscle and outcomes of SAH. Temporal muscle thickness (TMT) and area (TMA) have been useful indicators of sarcopenia [8]. To our knowledge, there have been no previous studies of the relationship between sarcopenia and outcomes of SAH. This is the first study to examine temporal muscle characteristics as indicators of sarcopenia

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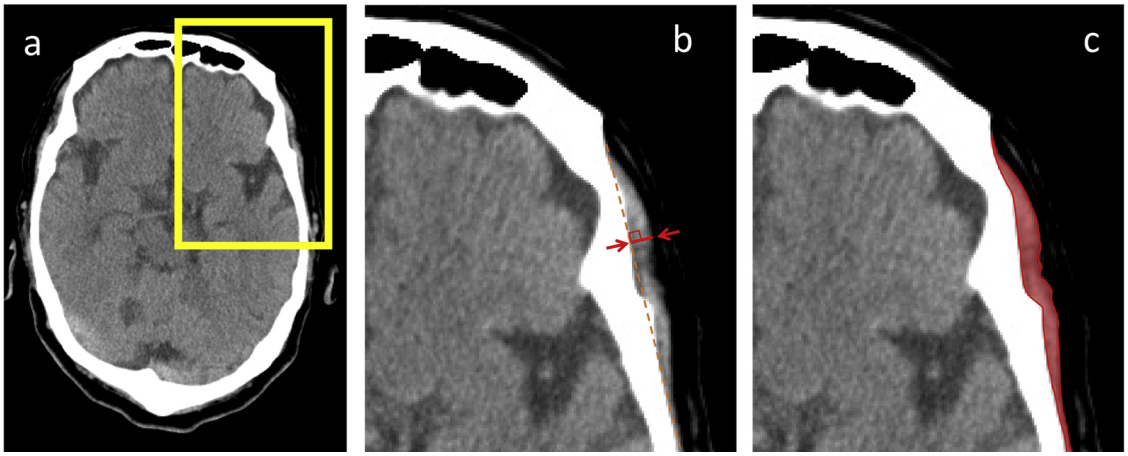

Fig. 1. Measuring temporal muscle thickness and area on the head computed tomography (CT) image. The slice is 5 mm above the superior wall of the orbit. (a) CT image representing temporal muscle thickness. (b) CT image representing the temporal muscle area. (c).

and outcomes of SAH.

2. Materials and methods

2.1. Study population

From the SAH databases of our hospital, we retrospectively retrieved the data from all of the 133 patients with aneurysmal SAH in all age groups who had been admitted from 2014 to 2018. We gained the agreements for this study from all of the patients. Besides, this study was approved by the hospital's research ethics committee. The diagnosis of SAH was based on the clinical history and the presence of SAH on computed tomography (CT).

General management of SAH was similar in all cases; all patients were first treated with nicardipine and kept normovolemic with normal blood pressure. A surgical indication was made regarding the Japanese Guidelines for the Management of Stroke 2015. Patients classified as World Federation of Neurological Surgeons (WFNS) grade [9] I-III were considered eligible to undergo aneurysm treatment, whereas those with WFNS grade IV and V were not regarded as suitable for such treatment except those with large intra-parenchymal hematoma. Coiling was considered when the aneurysm was in the posterior circulation or when coiling seemed superior to clipping. Patients with SAH of unverified etiology and due to arteriovenous malformation were excluded in this study. These direct surgery and endovascular surgery were performed within 72 h after onset.

All of the patients with SAH who had undergone aneurysm treatment received fasudil, cilostazol, and statin as appropriate after the operation. Intra-arterial infusion of fasudil was performed when necessary for treating symptomatic vasospasm. Also, a ventriculoperitoneal shunt was performed when hydrocephalus was observed.

The patients who did not receive treatment of the ruptured aneurysms were treated with medical treatment, including antihypertensive drugs, tube feeding, and antibacterial drugs. They undertook rehabilitation as much as their blood pressures were severely controlled.

2.2. Clinical variables

We collected data regarding physiological symptoms and laboratory data on admission for the patients included in this study, i.e., age, sex, body mass index (BMI), systolic blood pressure, lymphocyte, albumin, triglyceride, total cholesterol, low-density cholesterol, blood sugar, and hemoglobin A1c. Lymphocyte, albumin, and total cholesterol are known factors for controlling nutritional status (CONUT) score to assess the nutritional status of the patients [10]. The WFNS grading scale evaluated the clinical condition for SAH [9]. Patients were divided according to WFNS grade into the low-grade group (WFNS grade I-III) and high-grade group (WFNS grade IV and V). We recorded operative duration and whether clipping, coiling or conservative treatment was given.

We determined the Fisher CT scale, the presence of hydrocephalus, intraventricular hematoma, size of the aneurysm, location of the aneurysm, the TMT, and TMA based on the results of CT and computed tomography angiography (CTA) on admission. We used Aquilion ONE (Canon Medical Systems Corporation, Tochigi, Japan) to take CT and CTA images of 0.5 × 0.5 x 1.0 mm voxels. The slice thickness was reconstructed to 5 mm. The window width was adjusted to 300, and the window level was adjusted to 20. The TMT and TMA were measured by two investigators who did not know the patients' outcomes using SYNAPSE V 4.1.5 imaging software (Fujifilm Medical, Tokyo, Japan). The TMT was measured bilaterally perpendicular to the long axis of the temporal muscle at the slice 5 mm above the orbital roof, and calculated using averages of the left and right from three determinations of each side. The TMA was measured manually by tracing the outline of the temporal muscle on the same slice as used for measuring the TMT and computed by the software. The averages of the left and right of the TMT and TMA were calculated as a raw TMT and TMA (**Fig. 1**). We divided the raw TMT and TMA by the height, weight, and BMI to standardize the TMT and TMA. Both the raw TMT or TMA and the standardized TMT or TMA were used for analysis.

Symptomatic vasospasm was diagnosed by CT, CTA, magnetic resonance imaging (MRI), or magnetic resonance angiography with symptoms. CT or MRI diagnosed hydrocephalus with symptoms. Outcomes and ADL before hospitalization were assessed by the modified Rankin Scale (mRS) [11]. We dichotomized ADL before hospitalization and at discharge into favorable (mRS 0–2) or poor (mRS 3–6) about four weeks after admission in our acute care hospital.

2.3. Statistical analysis

About patients over 75 years old, the correlations between the clinical variables described above and the outcomes were analyzed using Fisher's exact test for categorical variables and Spearman's coefficient test for continuous variables. We regarded a Spearman correlation coefficient (r) (±)0.7-(±)1, (±)0.5-(±)0.7, (±)0.3-(±)0.5, and 0-(±)0.3 as a strong association, moderate association, weak association, and no association, respectively. A two-tailed $p < 0.05$ was considered statistically significant. The inter-rater reliabilities of the TMT and TMA were tested by intraclass correlation coefficients.

We performed similar investigations, as a subgroup analysis, on the correlation between the temporal muscle and the outcomes of the patients over 75 years old whose WFNS grade were I to III but also who

Table 1
Clinical characteristics and outcomes in 49 patients over 75 years old.

Age; mean (range)	83.5 (75-96)
Women:Men (%women)	42:7 (86%)
mRS before hospitalization, no. (%)	
mRS 0-2	39 (73%)
mRS 3	5 (10%)
mRS 4	6 (13%)
mRS 5	2 (4%)
WFNS grade, no. (%)	
Grade I	7 (15%)
Grade II	19 (40%)
Grade III	0 (0%)
Grade IV	6 (13%)
Grade V	16 (32%)
Low-grade (Grade I-III)	26 (45%)
Location of aneurysms, no. (%)	
Anterior circulation	40 (82%)
Posterior circulation	6 (12%)
Undetermined due to CPAOA	3 (6%)
mRS at discharge, no. (%)	
mRS 0-2	11 (27%)
mRS 3	3 (6%)
mRS 4	8 (16%)
mRS 5	9 (18%)
mRS 6	16 (33%)
Aneurysm treatment or conservative treatment, no. (%)	
Clipping	30
Coiling	4
Outcome after aneurysm treatment, WFNS grade I to V, no/total. (%)	
Favorable after clipping	12/30 (40%)
Favorable after coiling	1/ 4 (25%)
Outcome after aneurysm treatment, WFNS grade I to III, no/total. (%)	
Favorable after clipping	12/21 (57%)
Favorable after coiling	1/ 3 (33%)

CPAOA; cardiopulmonary arrest on arrival, mRS; modified Rankin Scale, WFNS grade; world federation of neurological surgeons grade, Favorable; modified Rankin Scale 0-2.

underwent aneurysm treatment. The sample size was so small ($n < 25$) in this group, that we used “the table of the critical values of Spearman’s rank correlation coefficient” to evaluate the r. $|r| > 0.407$ means significant when significance level (α) is 0.05, and $|r| > 0.344$ means significant when α is 0.10 [12].

Furthermore, we collected from the medical records premorbid condition, major complications, vasospasm, and hydrocephalus after the aneurysm treatment. The variables on the temporal muscle were compared between the patients with or without poor outcomes and major complications using Mann-Whitney U test. We conducted this analysis using version 24.0.0 of SPSS software. (IBM, NY, USA) (Table 1).

3. Results

3.1. Association between clinical variables and outcomes in all patients over 75 years old with SAH

The intraclass correlation coefficients (2, 2) about measuring TMT and TMA were 0.928 and 0.844 each. Of the all 49 patients over 75 years old with SAH, raw TMA, standardized TMT divided by weight, standardized TMA divided by height were significantly larger in the patients with favorable outcomes than that with poor outcomes ($p = 0.04, 0.01, 0.02$ each) (Fig. 2).

Besides, mRS before hospitalization, WFNS grade, lymphocyte, raw TMT, raw TMA, and size of the aneurysm showed significant correlations with mRS at discharge with Spearman’s coefficient test. In addition to raw TMT and TMA, standardized TMT divided by height, by weight, and standardized TMA divided by height were also correlated with mRS at discharge. The statistical meaning became stronger after standardization. Outcomes after aneurysm treatments were not statistically different between coiling and clipping in SAH patients whose WFNS grade were not only I to III but also I to V using Fisher's exact test ($p = 0.332, 0.392$, each) (Table 2). MRS 0–2, low-grade SAH, men, and absence of hydrocephalus were likely to have favorable outcomes (Table 3).

3.2. Characteristics of the SAH patients over 75 years old with aneurysm treatment, WFNS grade I to III

Of the 24 patients over 75 years old with SAH whose WFNS grade were I to III but also who underwent aneurysm treatment, the variables on the temporal muscle did not show significant correlation with mRS at discharge when the α is 0.05. However, raw TMT showed a weak correlation with mRS at discharge when the α is 0.10.

Eleven patients of the 24 patients had poor outcomes after the aneurysm treatment. Of the 11 patients, three had hydrocephalus after clipping and one after coiling, two had cerebral infarction after clipping, and ones had iliopsoas hematoma after clipping or rerupture after coiling. The other two after coiling and another after clipping did not suffer from complications, but they had dementia or sarcopenia, leading to poor outcomes. Of the 13 patients who had favorable outcomes, two had hydrocephalus, and one had vasospasm, another had urinary tract infection all after clipping. Two had reoperations due to coil compaction after coiling or bone infection after clipping. Standardized TMT divided by height, by weight, and TMA divided by weight were significantly larger in the patients with favorable outcomes than that with poor outcomes. The variables on temporal muscle were not associated with the occurrence of the major complications in all 24 patients (Table 4).

3.3. Complications of the SAH patients over 75 years old without aneurysm treatment

Two elderly patients with SAH whose WFNS grade were I to III did not undergo aneurysm treatment. The one died before treatment due to rerupture. The other’s family did not want her to have surgery due to her highly advanced age and moderate dementia. The patients whose WFNS grade were IV and V had poor outcomes due to primary brain injury, hydrocephalus, infection, or heart failure.

4. Discussion

4.1. Elderly patients with SAH

Japan is rapidly aging, and the cabinet office of Japan estimated our life expectancy would be over 90 years 50 years later. We presented the results of the 5-year retrospective study of the 49 patients aged over 75 years old with SAH, which accounted for 37% of all cases of SAH. Therefore, advanced age should not be the only reason that elderly patients with SAH cannot undergo aneurysm treatment.

A previous systematic review of 12 case series in a total of 815 patients reported that patients over 75 years old who were independent in ADL at discharge dominated from 0% to 80% and accounted for 35% on average [2]. In our study, the patients over 75 years old who were independent in ADL at discharge dominated 27%, so the results of our research seemed no significant difference compared to previous reports.

Aneurysm treatment can result in favorable outcomes in patients admitted in good condition [4]. Naturally, the indication for aneurysm treatment in cases with high-grade SAH should be considered carefully because of the poor prognosis. However, even elderly patients with low-grade SAH who undergo aneurysm treatment do not necessarily tend to have favorable outcomes. Therefore, elderly-specific clinical variables which are associated with favorable outcomes should be determined to facilitate decision making regarding aneurysm treatment to obtain favorable outcomes.

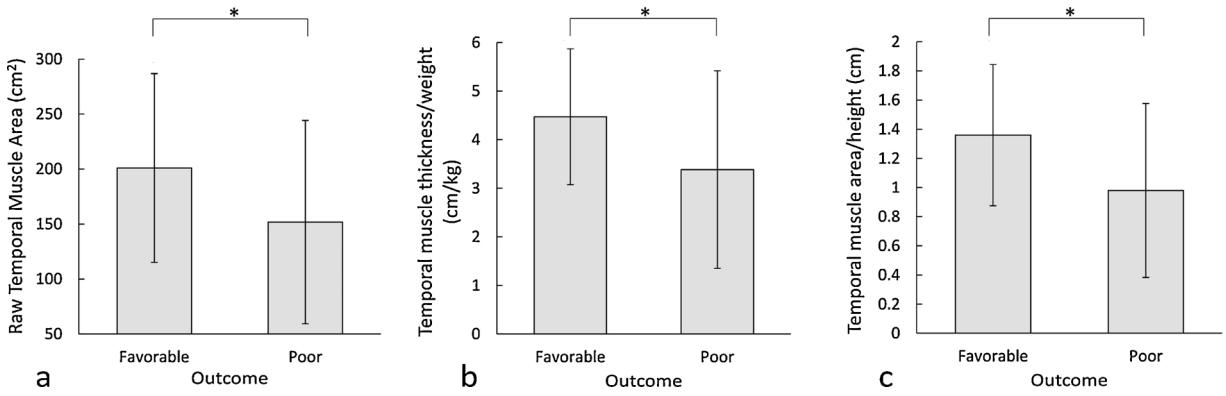

Fig. 2. Comparison of the raw temporal muscle area (TMA) (a), standardized temporal muscle thickness (TMT) divided by weight (b) and standardized TMA divided by height (c) in the favorable outcome and poor outcome groups of all the 49 patients over 75 years old with SAH. The error bars mean the standard deviations (SDs). The raw TMA (median, 201 cm^2 vs. 151 cm^2; SD, 85 cm^2 vs 92 cm^2; p = 0.04) was described in (a). The standardized TMT divided by weight (median, 4.47 cm/kg vs. 3.38 cm/kg; SD, 1.39 cm/kg vs 2.03 cm/kg; p = 0.01) in (b). The standardized TMA divided by height (median, 1.35 cm vs. 0.97 cm; SD, 0.48 cm vs 0.59 cm; p = 0.02) in (c). *; $p < 0.05$.

Table 2
Correlation between continuous variables and mRS at discharge in patients over 75 years old.

Variables	Coefficient	p value
mRS before hospitalization	0.346†	0.012*
WFNS grade	0.470†	0.0007*
Age	0.261	0.059
BMI	−0.179	0.21
- on admission		
Systolic blood pressure	0.174	0.22
Lymphocyte	0.329†	0.022*
Alb	−0.109	0.45
TG	0.039†	0.80
T-CHO	0.115	0.48
LDL	0.068	0.69
BS	0.197	0.184
HbA1c	−0.059	0.62
CONUT score	−0.05	0.72
Raw TMT	−0.302†	0.029*
Raw TMT/height	−0.342†	0.017*
Raw TMT/weight	−0.350†	0.012*
Raw TMT/BMI	0.056	0.69
Raw TMA	−0.306†	0.027*
Raw TMA/height	−0.374†	0.009*
Raw TMA/weight	−0.295	0.041
Raw TMA/BMI	−0.272	0.059
Size of aneurysm	−0.314†	0.026*
Operative duration	0.142	0.52

Alb; albumin, BMI; body mass index, BS; blood sugar, HbA1c; hemoglobin A1c, LDL; low-density cholesterol, mRS; modified Rankin Scale, T−CHO; total cholesterol, TG; triglycerides, TMA; temporal muscle area, TMT; temporal muscle thickness, WFNS grade; world federation of neurological surgeons grade, *; $p < 0.05$ by Spearman's coefficient test, †; |r| over 0.3.

Table 3
Relationship between categorical variables and favorable outcomes in patients over 75 years old.

Variables	Odds ratio	95% CI	p value
Independent (mRS0-2)	53‡	4.8 to 549	0.00007*
WFNS grade I - III	48‡	4.45 to 497	0.0002*
Men	5.15	1.14 to 23	0.044*
Fisher CT scale 1-2,	1.84	0.40 to 8.58	0.36
Frontal circulation	0.51	0.11 to 2.38	0.89
Absence of intraventricular hematoma	2.38	0.44 to 13	0.31
Absence of hypertension	0.83	0.21 to 3.5	0.56
Absence of dyslipidemia	3.84	0.25 to 3.2	0.69
Absence of diabetes mellitus	1.11	0.25 to 4.77	0.61
Absence of symptomatic vasospasm	1.39	0.23 to 8.1	0.56
Absence of hydrocephalus	21	2.79 to 145	0.0013*

CI; confident interval, CT; computed tomography, WFNS grade; world federation of neurological surgeons grade, *; $p < 0.05$ by Fisher's exact test, ‡; adjusted odds ratio.

4.2. Clinical variables of elderly patients with SAH focusing on temporal muscle

In elderly patients with SAH, initial poor neurological condition [13], over 75 years old [14], premorbid condition, complication after aneurysm treatment, and male sex [15] were shown to be risk factors for mortality. We identified the unfavorable outcomes at discharge in the SAH patients over 75 years old associated with women, hydrocephalus and correlated with high mRS before hospitalization, high WFNS grade, low lymphocyte, small raw TMT, small raw TMA, and large size of the aneurysm. To our knowledge, this is the first report about the association between sarcopenia as a potential prognostic factor and SAH outcome, focusing on the temporal muscle.

The temporal muscle was correlated with the outcomes of elderly patients with SAH, regardless of aneurysm treatment or conservative therapy. This is because the group of ADL-dependent patients with small TMT and TMA who had poor outcomes had a strong effect on the results. The temporal muscle was correlated with mRS before hospitalization, so the TMT and TMA of the patients with poor ADL tended to be low. Such ADL-dependent patients' WFNS grade would be severe because they were bedridden, incommunicable, or had dementia, so naturally, the mRS at discharge was poor. This result suggests that the premorbid ADL should be considered for surgical indication and that the patients whose premorbid ADL are independent can be a candidate for aneurysm treatment.

Furthermore, of course, modified Rankin Scale before the admission is more important than TMT and TMA to determine whether to perform aneurysm intervention. However, we think TMT and TMA would also be useful as objective and quantitative indicators for ADL rather than the subjective premorbid condition or medical information took from patient's family. Further study is needed to test the reliability of TMT and TMA.

Complications after aneurysm treatment are one of the poor prognostic factors in elderly [15]. In this study, however, even the patients with favorable outcomes suffered from complications such as reoperation, but they got them over and were discharged being independent. Besides, the outcome after aneurysm treatment was related to temporal muscle. This suggests that patients with large TMT and TMA could endure surgical stress or get over major complications, and temporal muscle would be a potential prognostic factor.

Table 4
Correlation between temporal muscle and mRS at discharge and present of major complication in patients over 75 years old with low-grade SAH after aneurysm treatment (subgroup analysis).

WFNS grade I to III, aneurysm treatment (n = 24)	Coefficient (r)	Critical value; ($\|r\| > 0.343$, $\alpha = 0.10$)
Raw TMT	−0.391	Significant
Raw TMT/height	−0.217	Not significant
Raw TMT/weight	0.127	Not significant
Raw TMA	−0.340	Not significant
Raw TMA/height	−0.149	Not significant
Raw TMA/weight	0.06	Not significant
WFNS grade I to III, aneurysm treatment, favorable outcome after aneurysm treatment (favorable; n = 13: poor; n = 11)	Mean	p value
Raw TMT (cm)	5.0:3.9	0.06
Raw TMT/height	0.033:0.026	0.02*
Raw TMT/weight (cm/kg)	0.11:0.09	0.02*
Raw TMA (cm^2)	204:135	0.12
Raw TMA/height (cm)	1.33:0.89	0.06
Raw TMA/weight (cm^2/kg)	4.35:3.16	0.04*
WFNS grade I to III, aneurysm treatment, major complication after aneurysm treatment (absent; n = 10: present; n = 14)	Mean	p value
Raw TMT (cm)	4.6:4.3	0.52
Raw TMT/height	0.029:0.029	0.80
Raw TMT/weight (cm/kg)	0.09:0.10	0.66
Raw TMA (cm^2)	187 :144	0.10
Raw TMA/height (cm)	1.21:0.97	0.46
Raw TMA/weight (cm^2/kg)	3.94:3.52	0.46

mRS; modified Rankin Scale, TMA; temporal muscle area, TMT; temporal muscle thickness, WFNS grade; world federation of neurological surgeons grade, α; significance level, *; $p < 0.05$ by Mann Whitney U test.

4.3. Sarcopenia as a prognostic factor

Sarcopenia has also been reported as a strong predictor of poor prognosis of some diseases such as chronic obstructive pulmonary disease and heart failure [16,17]. Besides, higher skeletal muscle mass may protect against ischemic stroke [18], and the risk for intracranial arterial stenosis is lower in people with higher muscle mass [19]. Furthermore, sarcopenia is related to medium-term outcome in asymptomatic patients after carotid artery stenting [20] and poor outcome after traumatic brain injury [21]. Many studies regarding the association between sarcopenia and the outcomes used psoas muscle cross-sectional area at the level of the third lumbar vertebra [22], muscle mass, gait speed, handgrip strength as indicators of sarcopenia [23]. Recently, the temporal muscle has attracted notice as a useful indicator of sarcopenia [8], and as an indicator of both prognoses of brain metastasis [24,25] and predictor of major complications after surgery [26]. We cannot measure the gait speed, and hand grip strength of SAH patients on admission concerning of rerupture. Patients with SAH undergo head CT, so we can easily and safely obtain information about the temporal muscle on the CT image. Therefore, we focused on the temporal muscle in the present study.

Sarcopenia is related to malnutrition and aging [27]. Lymphocyte, one of the factors indicating nutrition status [10], was also one of the prognostic factors for SAH outcome in our study. This also supports our hypothesis that patients with sarcopenia and SAH tend to have poor outcomes due to malnutrition.

4.4. Limitation

Our results were statistically meaningful, but the statistical power was weak due to the small sample size. We need about 300–1200 population to obtain our results with sufficient statistical power (= 0.80) and fewer errors in correlation coefficient using Spearman's coefficient test [28,29]. However, the data has been rarely reported on the elderly who underwent treatment for the ruptured aneurysm, and the sample size in the previous reports ranged 10–333 [2,4,5,13–15,30]. Therefore we considered our study worth to be reported. Our findings were preliminary, so further studies are needed with large sample sizes and another long term endpoint such as mRS not only at discharge but also after six months.

The previous studies reported temporal muscle bulk of female patients is lower than that of male [8,24], but the authors concluded that the prognostic role of temporal muscle was independent of gender [24,25]. Our data on temporal muscle showed similar gender difference, and further investigation by gender with large sample size is needed.

Systemic CT and MRI are gold standards for estimating muscle mass in research [23], but it is difficult to take a systemic scan to SAH patients. Alternative factors such as arm and calf circumference or skinfold thickness indicating sarcopenia would be taken for further study.

The accuracy of TMT and TMA measurement was not established. Ranganathan [8] and Rinkinen [26] used image analysis and engineering software to measure temporal muscle. Further [25] did not use image analysis and engineering software, but used MRI and measured TMT perpendicular to the long axis of the temporal muscle at the level of the orbital roof. Here, we used CT to measure TMT and TMA. Measurement using CT images is easy because we routinely perform head CT and do not require special software for the analysis. However, TMA was measured manually by tracing the outline of the temporal muscle, so there may be a lack of accuracy and reproducibility. Therefore we calculated them using averages of the left and right from three determinations of each side by two investigators.

5. Conclusions

Aneurysm intervention should be considered when SAH patients over 75 years old do not suffer from sarcopenia. Temporal muscle would indicate premorbid ADL and be potentially useful to decide surgical indication and to predict outcomes after aneurysm treatment.

Notes

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.clineuro.2019.105535.

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