Original Article

Premorbid sarcopenia and functional outcome after acute stroke: a meta-analysis

Yunpan Li MD[1], Mei Hong MD[2], Hong Shi MD[1]

[1]*Department of Geriatrics, Shanghai Putuo District Liqun Hospital, Shanghai, China*
[2]*Department of Respiratory Diseases, Shanghai Putuo District Liqun Hospital, Shanghai, China*

Background and Objectives: Sarcopenia is prevalent in patients with stroke. However, the relationship between sarcopenia and poor functional outcome of patients with acute stroke remains unknown. A systematic review and meta-analysis was performed to evaluate the above association. **Methods and Study Design:** Observational studies which evaluated the influence of sarcopenia on functional outcome in patients with acute stroke were retrieved by search the PubMed, Embase, Cochrane Library, and Web of Science databases. A poor functional outcome was defined as modified Rankin scale (mRS) of two or more points during follow-up. Two authors independently collected the data of study characteristics and outcomes. A random-effects model was used to pool the results via incorporating the influence of possible between-study heterogeneity. **Results:** Nine datasets from seven cohort studies contributed to the meta-analysis. A total of 1774 patients with stroke were included, and 481 (27.1%) of them had sarcopenia. Compared to patients without sarcopenia, those with sarcopenia were associated with a higher risk of poor functional outcome during follow-up duration up to 6 months after stroke onset (odds ratio: 2.42, 95% confidence interval: 1.76 to 3.33, $p < 0.001$) with mild heterogeneity ($I^2 = 23\%$). Subgroup analyses according to study design (prospective versus retrospective), sex of the patient, type of stroke (ischemic or mixed), diagnostic methods for sarcopenia, follow-up duration and cutoff scores for mRS showed consistent results (*p* for subgroup analyses all > 0.05). **Conclusions:** Sarcopenia may be associated with poor functional outcome in patients with acute stroke.

Key Words: sarcopenia, stroke, function outcome, modified ranking scale, meta-analysis

INTRODUCTION

Despite of the continuous efforts in the primary and secondary prevention of cardiocerebrovascular diseases, stroke remains one of the most important causes of morbidity and mortality of the global population, particularly in the older people.[1-3] With the accelerating of the population aging worldwide, it could be estimated that the numbers of patients with stroke will continuously increase in upcoming decades.[4] According to the etiology, stroke could be classified as ischemic and hemorrhagic.[5] Although acute ischemic stroke (AIS) accounts for the majority cases of stroke, patients with hemorrhagic stroke, such as those with intracerebral hemorrhage (ICH), usually have poor prognosis.[6] Due to the complexity of the etiology and clinical progression of stroke, it is important to determine the prognostic factor which is associated with the functional outcome of these patients.[7]

It has been shown that sarcopenia, a generalized loss of skeletal muscle mass with aging,[8] is associated with frailty, overall functional impairment, and poor survival in older population.[9] It has been confirmed that disability of extremities related to stroke may lead to sarcopenia in patients with stroke.[10] A recent systematic review showed that the overall prevalence of sarcopenia in survivors of stroke (stroke-induced sarcopenia) was 42%.[11] On the other hand, due to the close correlation of sarcopenia with aging and the high incidence of stroke in older people, considerable patients with acute stroke may already have sarcopenia at the onset of stroke (premorbid sarcopenia).[12] Therefore, it is important to determine if sarcopenia in patients with acute stroke is associated with poor prognosis.[13] Accordingly, in this systematic review and meta-analysis, we aimed to evaluate the influence of sarcopenia on the risk of poor functional outcome during follow-up in patients with acute stroke.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[14,15] and the Cochrane's Handbook[16] guideline was followed in the conceiving, conducting, and reporting the study.

Search of databases

Studies were retrieved by search of the electronic databases including PubMed, Embase, Web of Science, Cochrane Library, and Web of Science databases from

Corresponding Author: Dr Yunpan Li, Department of Geriatrics, Shanghai Putuo District Liqun Hospital, 910 Taopu Road, Putuo District, Shanghai 200333, China
Tel: 86-22-52780030
Email: lyp_sh2988@21cn.com
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the inception to January 10, 2023, with the combined key terms of (1) "sarcopenia" OR "muscle wasting" OR "muscle loss" OR "muscular atrophy" OR "muscle depletion" OR "sarcopaenia" OR "sarcopenic" OR "presarcopenia" OR "sarcopaenic" OR "lean body mass" OR "cross-sectional muscle area" OR "skeletal muscle depletion" OR "muscle mass" OR "muscle index"; (2) "stroke" OR "transient ischemic stroke" OR "TIA" OR "cerebral infarction" OR "cerebrovascular infarction" OR "intracerebral hemorrhage" OR "intracranial hemorrhage"; and (3) "functional outcome" OR "prognosis" OR "modified Rankin Scale" OR "function outcome". The search was restricted to clinical studies involving patients with stroke and published in English. The reference lists of the relevant original and review articles were also manually screened for possible related studies. Only studies published as full-length articles in peer-reviewed journals were considered to be eligible for the meta-analysis.

Study inclusion and exclusion criteria

The inclusion criteria were developed according to the aim of the meta-analysis, with the recommended PICOS criteria.

P (patients): Adult patients diagnosed as acute stroke, including AIS and acute ICH.

I (exposure): Patients the sarcopenia at the onset of stroke.

C (control): Patients without sarcopenia at the onset of stroke. The diagnostic methods and criteria were in accordance with the strategies used in the original studies.

O (outcomes): Incidence of poor functional outcome during follow-up in acute stroke patients with versus without sarcopenia at baseline. A poor functional outcome was defined as AIS patients with functional dependency as evaluated by modified Rankin scale (mRS) of two or more points during follow-up.

S (study design): Observational studies with longitudinal follow-up, which included cohort studies, nested case-control studies, and post-hoc analysis of clinical trials. Reviews, editorials, meta-analyses, studies including patients not with stroke, studies including patients with non-acute stroke, or studies that did not report the outcome of poor functional outcome were excluded. For studies with the overlapped population, the one with the largest sample size was included.

Data collection and quality assessing

The literature search, data collection, and study quality assessment were independently conducted by two authors. If discrepancies occurred, the corresponding author was contacted for discussion to reach the consensus. We collected data regarding study information, participant characteristics (age, sex, and type of stroke, methods and criteria for the diagnosis of sarcopenia, follow-up duration, definitions of the outcome, and variables incorporated in the multivariate regression analyses. Study quality was assessed via the Newcastle–Ottawa Scale (NOS)[17] with scoring regarding the criteria for participant selection, comparability of the groups, and the validity of the outcomes. The scale ranged between 1-9 stars, with larger number of stars presenting higher study quality.

Statistical analyses

The association between sarcopenia and the incidence of poor functional outcome after stroke was summarized as odds ratios (ORs) and the 95% confidence intervals (CIs). For studies that analyzed the above association with multiple regression models, data with the most adequately adjusted model was extracted for the meta-analysis. Using the data of 95% CIs or *p* values, data of ORs and the standard errors (SEs) could be calculated, and a subsequent logarithmical transformation was conducted to keep stabilized variance and normalized distribution. Between-study heterogeneity was examined with the Cochrane Q test and the estimation of I^2 statistic.[18] An $I^2 > 50\%$ reflects the significant heterogeneity. A random-effects model was applied to combine the results by incorporating the influence of heterogeneity.[16] Sensitivity analysis by excluding one dataset at a time was performed to evaluate the influence of individual study on the results of the meta-analysis.[19] Subgroup analyses were performed to evaluate the influence of study characteristics on the outcome. By construction of the funnel plots, the publication bias was estimated based on the visual judgment of the symmetry of the plots, supplemented with the Egger's regression asymmetry test.[20] The RevMan (Version 5.1; Cochrane Collaboration, Oxford, UK) and Stata software (version 12.0; Stata Corporation, College Station, TX) were applied for these analyses.

RESULTS

Literature search

The flowchart of literature search and study inclusion was displayed in Figure 1. In summary, 471 studies were obtained in the initial database search, and 55 were removed for duplications. Subsequently, 416 studies were screened with titles and abstracts, and 389 were excluded mainly because they were not relevant to the objective of the meta-analysis. Therefore, 27 studies underwent full-text review, and 20 were excluded for the reasons listed in Figure 1. Finally, seven cohort studies[21-27] were available for the meta-analysis.

Study characteristics

Overall, seven cohort studies including 1774 patients with stroke were included,[21-27] and 481 (27.1%) of them had sarcopenia. These studies were published between 2019 and 2022, and performed in Japan, Korea, and China. Regarding study design, three of them were prospective,[21,24,25] the other four were retrospective.[22,23,26,27] As for the diagnosis, four studies included patients with AIS only,[22,24,26,27] while the remaining three included patients with AIS and ICH.[21,23,25] The sample sizes of the included studies were 107 to 568. The mean ages were 57 to 76 years, and the proportions of men were 53 to 66%. Sarcopenia was diagnosed according to the European Working Group on Sarcopenia in Older People (EWGSOP) criteria with grip strength in one study,[23] using the Asian Working Group for Sarcopenia (AWGS) criteria with skeletal muscle mass index (SMI) in three studies,[22,24,26] and with tools such as SARC-F questionnaire[21,25] and measuring the temporal muscle thickness[27] in other three studies. The follow-up durations were from hospitalization to 6 months after disease onset. In most studies, a poor func-

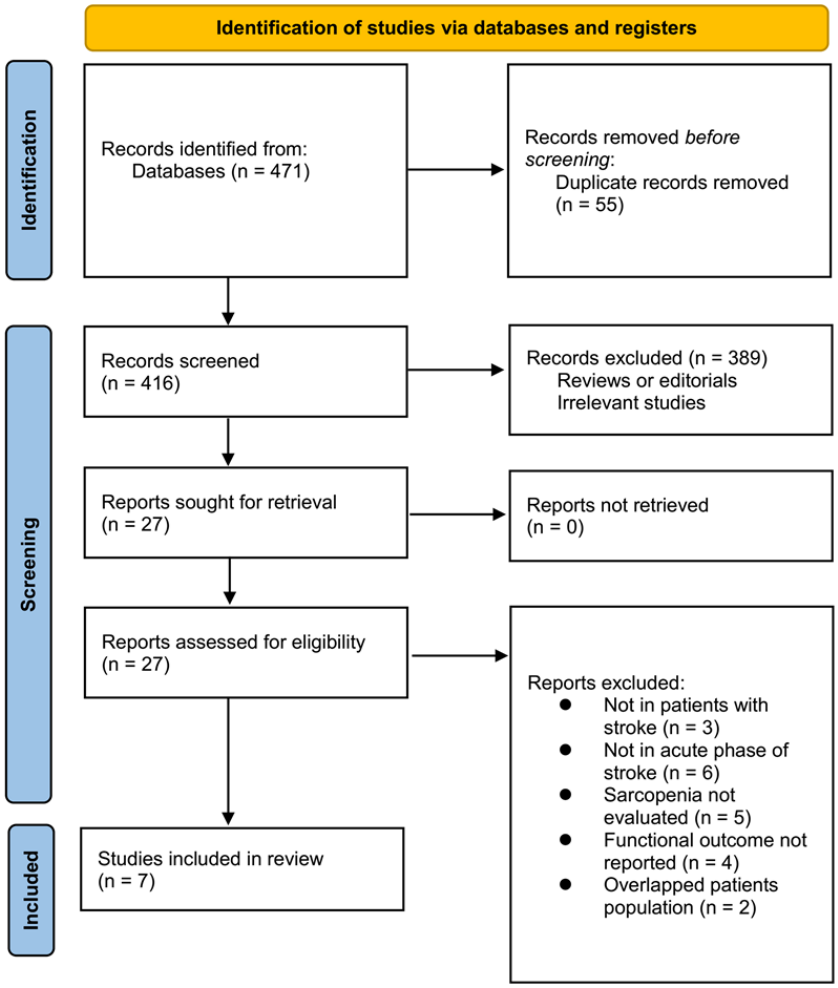

Figure 1. Diagram of database search and study inclusion

Table 1. Characteristics of the included studies

Study	Design	Country	Stroke type	Sample size	Mean age (years)	Male (%)	Diagnosis of sarcopenia
Nozoe 2019	PC	Japan	AIS and ICH	152	76	53.3	SARC-F
Jang 2020	RC	Korea	AIS and ICH	194	64.3	59.3	EWGSOP (grip strength)
Abe 2020	RC	Japan	AIS	107	76	66.4	AWGS (SMI)
Ohyama 2020	PC	Japan	AIS	164	57.4	65.9	AWGS (SMI)
Nozoe 2021	PC	Japan	AIS and ICH	324	76	57.7	SARC-F
Lee 2022	RC	Korea	AIS	568	65.5	64.6	AWGS (SMI)
Li 2022	RC	China	AIS	265	67.4	62.6	TMT

Study	No. of patients with sarcopenia	Follow-up duration	Definition of poor functional outcome	Variables adjusted
Nozoe 2019	27	3 months	mRS 4~6	Age, sex, previous stroke, dyslipidemia, and NIHSS
Jang 2020	81	6 months	mRS 4~6	Age, sex, FOIS, and malnutrition
Abe 2020	32	At discharge	mRS 4~6	Age, sex, length of hospital stay, NIHSS, previous stroke
Ohyama 2020	101	At discharge	mRS 3~6	Age, sex, NIHSS, and PVH
Nozoe 2021	61	3 months	mRS 4~6	Age, sex, pre-stroke disability, NIHSS, and malnutrition
Lee 2022	48	3 months	mRS 2~6	Age, sex, albumin, and initial NIHSS score
Li 2022	131	At discharge	mRS 4~6	Age, sex, BMI, and NIHSS

PC, prospective cohort; RC, retrospective cohort; AIS, acute ischemic stroke; ICH, intracerebral hemorrhage; EWGSOP, the European Working Group on Sarcopenia in Older People; AWGS, the Asian Working Group for Sarcopenia; SMI, skeletal muscle mass index; TMT, temporal muscle thickness; mRS, the modified Rankin scale; FOIS, the Functional Oral Intake Scale; NIHSS, National Institutes of Health Stroke Scale; PVH, periventricular hyperintensity

Table 2. Study quality evaluation via the Newcastle-Ottawa Scale

Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome not present at baseline	Control for age and sex	Control for other confounding factors	Assessment of outcome	Enough long follow-up duration	Adequacy of follow-up of cohort	Total
Nozoe 2019	1	1	0	1	1	1	1	1	1	8
Jang 2020	0	1	1	1	1	1	1	1	1	8
Abe 2020	0	1	1	1	1	1	1	0	1	7
Ohyama 2020	1	1	1	1	1	1	1	0	1	8
Nozoe 2021	1	1	0	1	1	1	1	0	1	8
Lee 2022	1	1	1	1	1	1	1	1	1	9
Li 2022	1	1	0	1	1	1	1	0	1	7

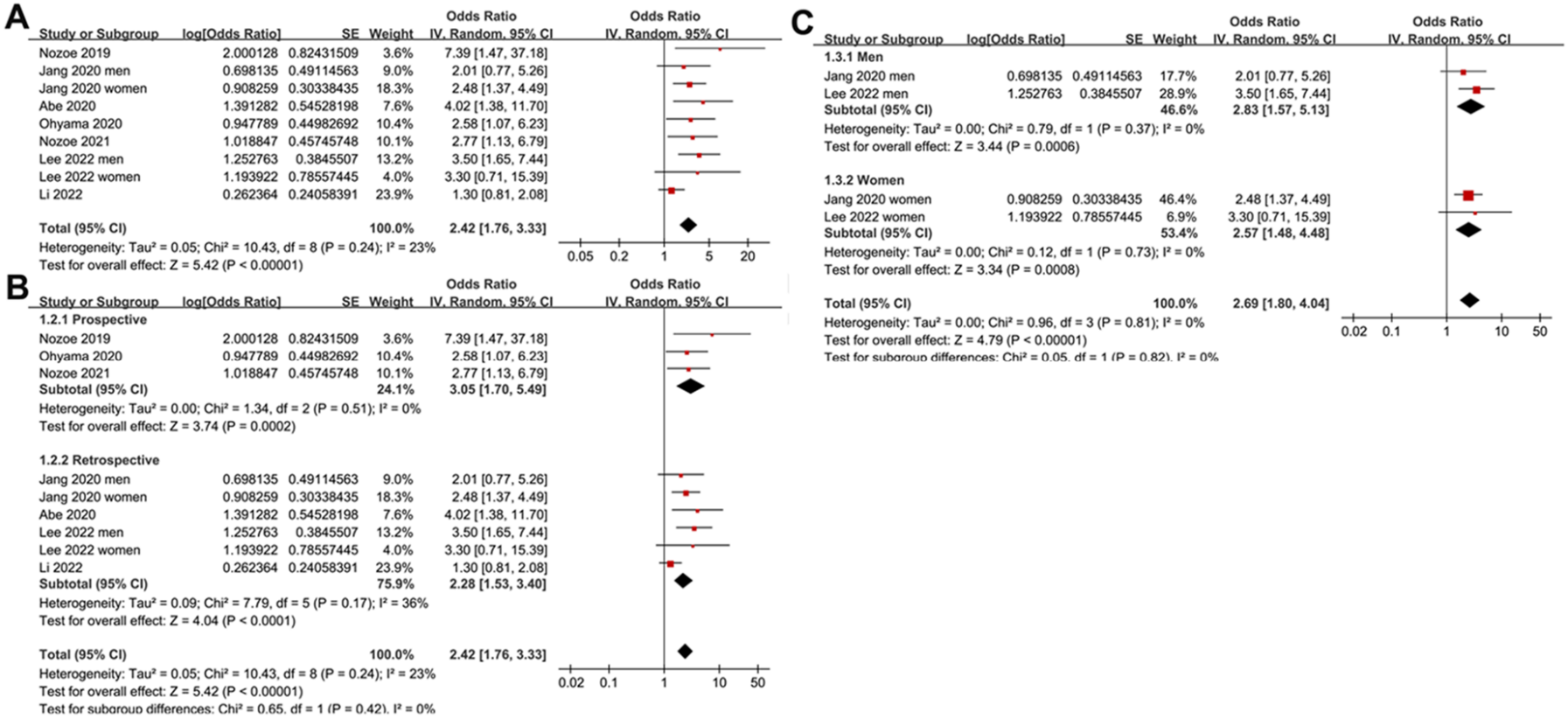

Figure 2. Forest plots for the meta-analyses of sarcopenia and poor functional outcome of patients with acute stroke. A, overall meta-analysis; B, subgroup analysis according to study design; and C, subgroup analysis according to the sex of the patients.

tional outcome was defined as the mRS of 4~6,[21-23,25,27] while in other two studies, it was defined as the mRS of 2~6[26] and 3~6,[24] respectively. For all the included studies, multivariate analyses were used to evaluate the association between sarcopenia and the incidence of poor functional outcome after stroke, after adjustment of potential confounding factors such as age, sex and the National Institutes of Health Stroke Scale (NIHSS) at admission etc. The NOS of the included studies were from seven to nine stars, suggesting generally good study quality (Table 2).

Association between sarcopenia and functional outcome after stroke

Since two studies reported the association according to the sex of the patients, these datasets were included in the meta-analysis independently,[23,26] which made nine datasets from seven studies available for the meta-analysis. Pooled results showed that compared to patients without sarcopenia, those with sarcopenia were associated with a higher risk of poor functional outcome during follow-up duration (OR: 2.42, 95% CI: 1.76 to 3.33, $p < 0.001$; Figure 2A) with mild heterogeneity (p for Cochrane Q test = 0.24, I^2 = 23%). Sensitivity analysis by excluding one dataset at a time showed similar results (OR: 2.27 to 2.90, p all < 0.05). Subgroup analyses showed consistent results in prospective and retrospective cohorts (Figure 2A), in men and women (Figure 2B), in patients with AIS or AIS/ICH (Figure 3A), in studies with different diagnostic criteria for sarcopenia (Figure 3B), in studies with different follow-up durations (Figure 4A), and in studies with different cutoffs of mRS (Figure 4B, p for subgroup analyses all > 0.05).

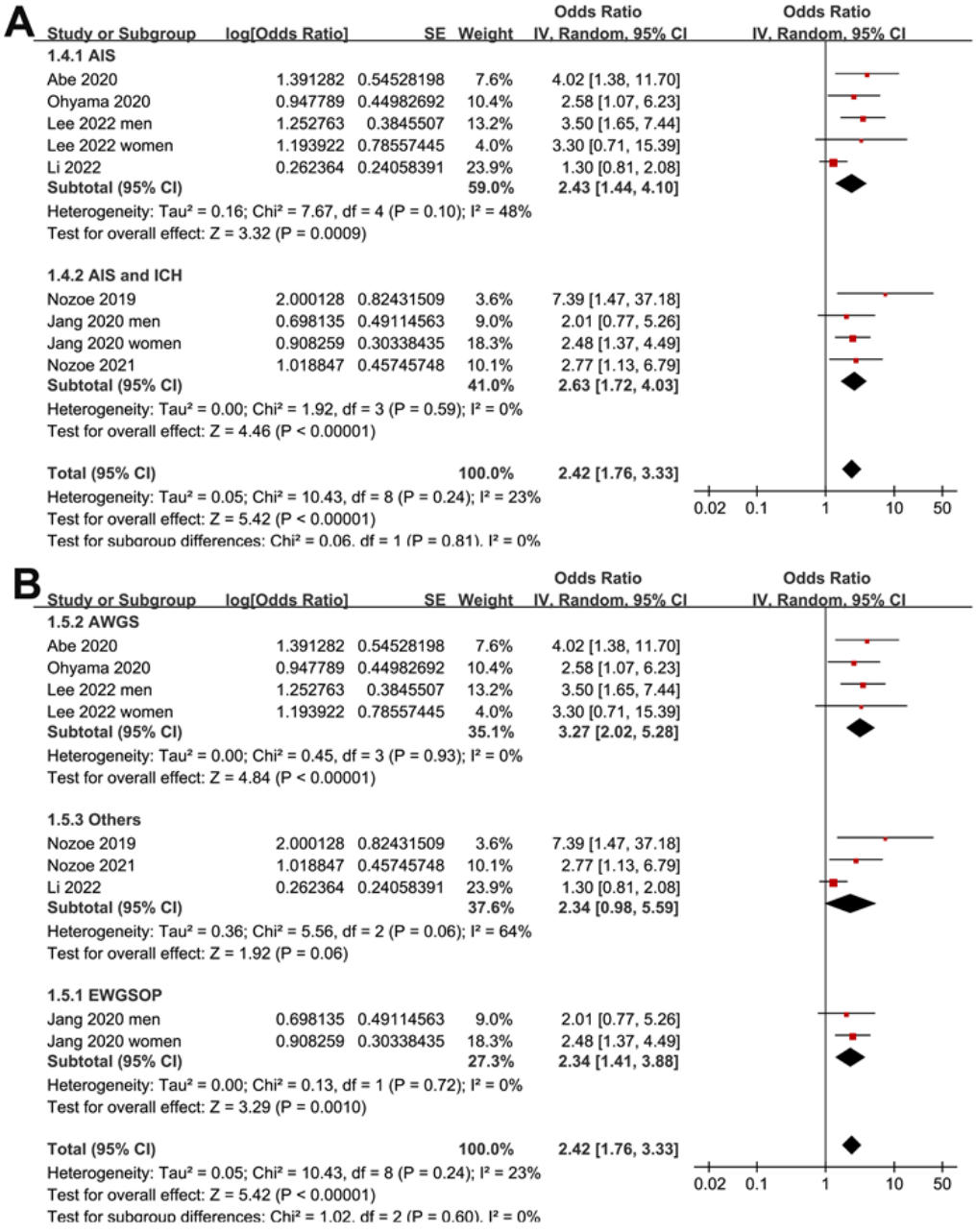

Figure 3. Forest plots for the subgroup analyses of sarcopenia and poor functional outcome of patients with acute stroke. A, subgroup analysis according to diagnosis; and B, subgroup analysis according to the criteria to define sarcopenia

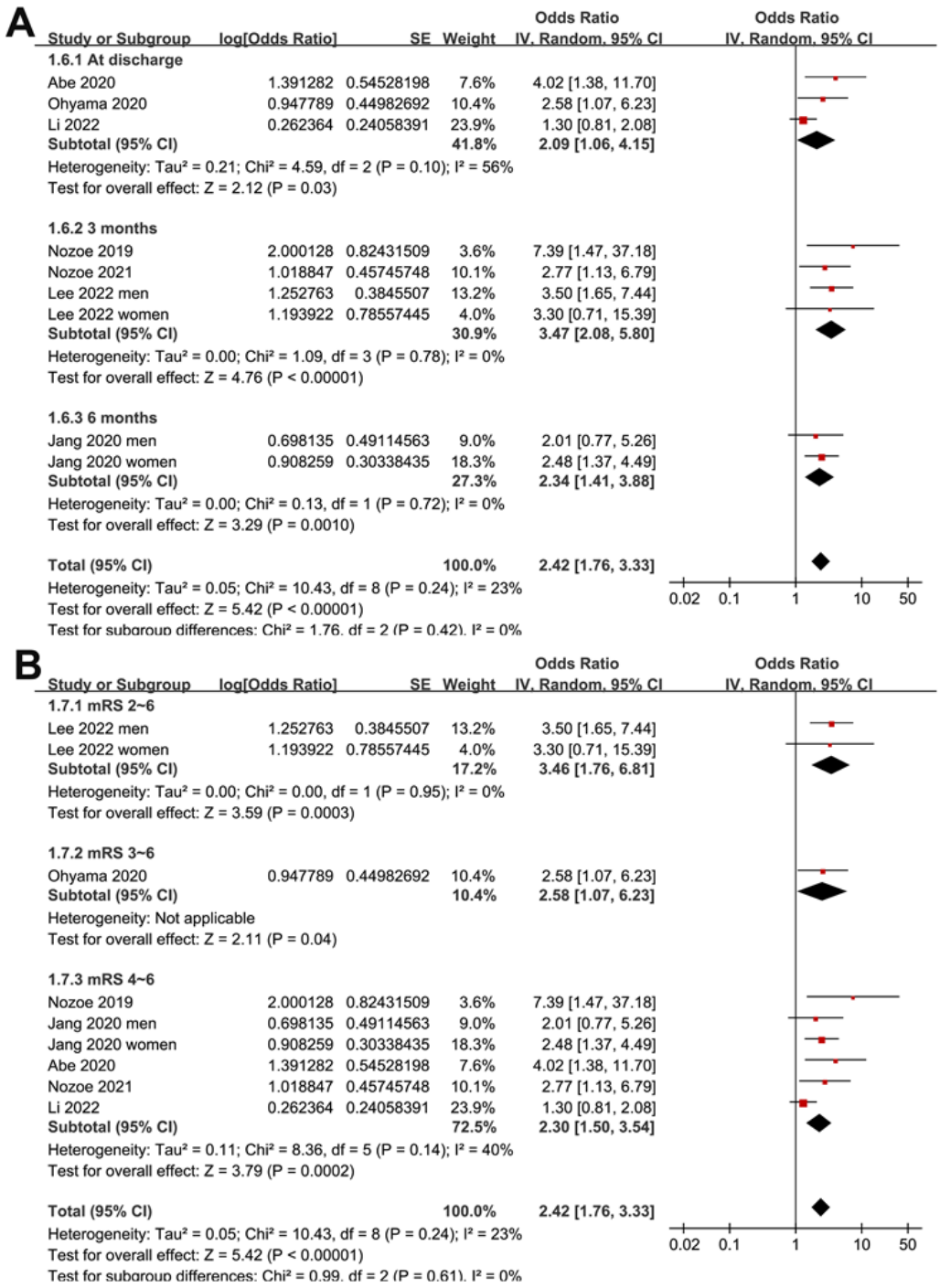

Figure 4. Forest plots for the subgroup analyses of sarcopenia and poor functional outcome of patients with acute stroke. A, subgroup analysis according to follow-up duration; and B, subgroup analysis according to cutoffs of mRS

Publication bias

Figure 5 represents the funnel plots for the associations between sarcopenia and the risk of poor functional outcome in patients with acute stroke. Visual inspection revealed symmetry of the plots, reflecting a low risk of publication biases. The Egger's regression tests also indicated low risk of publication biases ($p = 0.52$).

DISCUSSION

Since both sarcopenia and stroke are related to aging, we observed in this study of meta-analysis if premorbid sarcopenia is associated with the poor functional outcome in patients with acute stroke. By searching four commonly used electronic databases, we obtained nine datasets from seven eligible studies. The results showed that compared to those without sarcopenia at baseline, patients with sarcopenia and acute stroke were associated with a higher incidence of poor functional outcome during the follow-up duration up to six months after stroke onset. The stability and robustness of the finding was further confirmed by consistent results of multiple sensitivity and subgroup analyses, according to the study design, patient sex, type of stroke, criteria for determining sarcopenia, follow-up duration, and cutoff of mRS to define poor functional outcome. Taken together, results of the meta-analysis demonstrate that sarcopenia may be associated with poor functional outcome in patients with acute stroke.

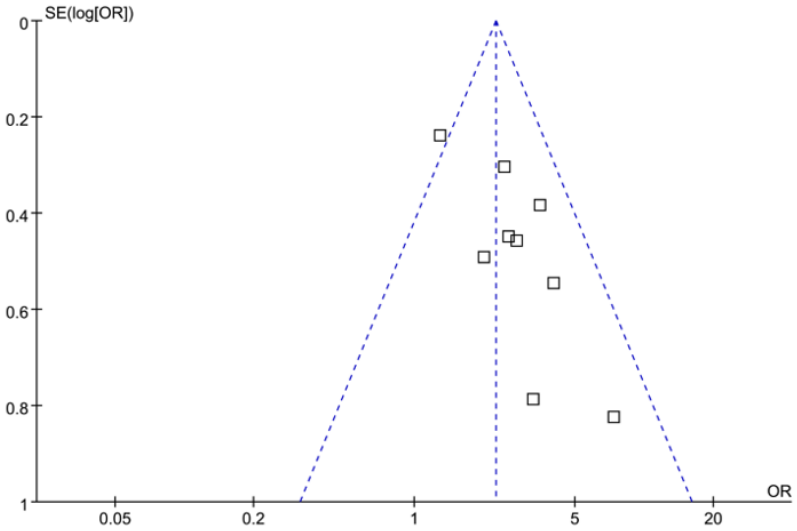

Figure 5. Funnel plots for the publication bias of the meta-analyses

To the best of our knowledge, this may be the first systematic review and meta-analysis which summarized the current evidence of the association between sarcopenia and poor functional outcome in patients with acute stroke. There are several methodological strengths of the meta-analysis which should be noticed before the results are interpreted. Frist, an extensive literature search was performed four commonly used English electronic databases, which provided the up-to-date literatures on this topic. Second, all the included studies were cohort studies, which could provide a longitudinal relationship between premorbid sarcopenia and poor functional outcome in patients with acute stroke. This is important because stroke itself could also lead to disability and sarcopenia. Third, in all the studies, the relationship between sarcopenia and poor functional outcome was analyzed with a multivariate regression model, which therefore could suggest a potentially independent association. Finally, consistent results in multiple subgroup analyses could also suggest that the relationship between sarcopenia and poor functional outcome was independent of the study characteristics involved in the subgroup analyses. Taken together, these findings confirmed that sarcopenia may be an independent predictor of poor functional outcome of patients with acute stroke.

The potential mechanisms underlying the association between sarcopenia and poor functional outcome after stroke may be multifactorial. An early study in elderly patients with acute stroke showed that the presence of pre-stroke sarcopenia was correlated with the severity of stroke, as indicated by the NIHSS, even after adjusting for various confounding factors.[28] Subsequent studies in patients hospitalized after acute stroke showed that sarcopenia defined as low trunk and appendicular skeletal muscle mass index at admission was independently associated with impaired swallowing function and eating activities,[29] as well reduced activities of daily living[30] at discharge. Early neurological deterioration (END) is an independent predictor of poor functional outcome in patients with acute stroke.[31] A recent study showed that premorbid sarcopenia was independently associated with END in patients with AIS, which may also partly explain the results of the meta-analysis.[13] In addition, a long-term follow-up study showed that sarcopenia at baseline was independently associated with a higher risk of recurrent cerebrovascular events,[32] which may be an underlying mechanism. Pathologically, people with sarcopenia, as compared to those with normal muscular volume and strength, are associated with higher systematic inflammation[33] and oxidative stress,[34] while both of which have been linked to the aggravated neurologic dysfunction during stroke.[35,36] Studies are warranted in the future to determine the key molecular mechanisms underlying the association between sarcopenia and deteriorated neurologic function in stroke.

This study also has limitations. First, multiple methods were used to define sarcopenia among the included studies. To the best of our knowledge, no consensus has been reached regarding the gold diagnostic criteria for sarcopenia for patients with acute clinical conditions, such as stroke. Although the subgroup analysis showed no significant difference, studies are needed to determine the optimal methods and criteria for determining sarcopenia in patients with acute stroke. In addition, the number of the included studies for the meta-analysis is small. Results of the meta-analysis and subgroup analyses should be interpreted with caution and better to be validated in large-scale prospective studies. Moreover, although multivariate analyses were applied among the included studies, we could not exclude the possibility that there are still unadjusted factors which may confound the association between sarcopenia poor functional outcomes after stroke. Finally, as a meta-analysis of observational studies, the causative relationship between sarcopenia and poor prognosis of stroke could not be concluded on the basis of the results.

Conclusions

To sum up, results of the meta-analysis indicate that premorbid sarcopenia may be a potential predictor of poor functional outcome in patients with acute stroke. Studies are needed to determine the optimal methods for the diagnosis of sarcopenia in patients with acute stroke,

and to evaluate if improve sarcopenia in the acute phase of stroke could improve the prognosis of the patients.

AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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