European Review for Medical and Pharmacological Sciences 2022; 26: 610-622

Critical prognostic factors for poststroke dysphagia: a meta-analysis

C.H. LIU[1], M. HUO[2], H.H. QIN[2], B.L. ZHAO[2]

[1]Department of Clinical Nursing, Jiamusi College, Heilongjiang University of Chinese Medicine, Jiamusi, Heilongjiang, P.R. China
[2]Department of Clinical Nursing, School of Nursing, Dalian University, Dalian, Liaoning, P.R. China

Abstract. – OBJECTIVE: Poststroke dysphagia (PSD) is one of the most significant problems after stroke. The prognosis of dysphagia is closely related to the outcomes of stroke. This meta-analysis aimed at identifying and evaluating critical predictors of prognosis for PSD.

MATERIALS AND METHODS: Electronic databases were searched for relevant case-control and cohort studies in which the prognostic factors of PSD were reported. The methodological quality of the studies was assessed using the Newcastle-Ottawa Scale. Review Manager 5.3 was used to calculate odds ratios (OR) and their 95% confidence intervals (CI) of the included factors and to perform heterogeneity and sensitivity analyses. Stata 15.1 was used to evaluate publication bias.

RESULTS: Eighteen of 3132 total studies were finally included in this meta-analysis. Ten predictors of PSD were identified, including 2 protective factors and 8 risk factors. Early intervention (OR=0.75, 95% CI=0.61-0.93) and an MRS (modified Rankin scale) score of 0 before onset (OR=0.58, 95% CI=0.47-0.71) were related to a better prognosis of PSD. The risk factors ranked by pooled OR values were aspiration (OR=7.64, 95% CI=5.94-9.82), brainstem injury (OR=4.82, 95% CI=3.01-7.72), severity of stroke (OR= 3.06, 95% CI=1.69-5.53), bihemispheric injury (OR=3.0, 95% CI=1.67-5.40), older age (OR=1.75, 95% CI=1.50-2.04), malnutrition (OR=1.36, 95% CI=1.22-1.53), severe dysphagia on admission (OR=1.16, 95% CI=1.03-1.29), and reduced level of consciousness (OR=1.03, 95% CI=1.00-1.07).

CONCLUSIONS: Prognostic factors for a good outcome of PSD included early intervention and an MRS score of 0 before onset. Aspiration, brainstem injury, severe stroke and bihemispheric injury are the four most significant predictors of poor prognosis in PSD. Identifying these prognostic factors should help clinicians to better detect patients at risk and provide effective interventions for PSD.

Key Words:
Stroke, Dysphagia, Deglutition disorders, Prognosis factors, Meta-analysis.

Abbreviations
Post-stroke dysphagia (PSD); Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA); Newcastle-Ottawa Scale (NOS); Activities of daily life (ADL); National Institutes of Health Stroke Scales (NIHSS); Modified Rankin Scale (MRS); Odds ratios (OR); Confidence intervals (CI).

Introduction

Poststroke dysphagia (PSD) is one of the most common complications of stroke. Approximately 30%-80% of patients suffer from dysphagia after stroke, depending on the methods of evaluation, the lesion location, and the elapsed time period from the onset of the stroke[1-5]. Previous studies[4,6] have demonstrated that PSD is a significant independent risk factor affecting the prognosis of stroke patients. The incidences of pulmonary infection, malnutrition, dehydration and self-care disorders in PSD patients were three times higher than those in patients without PSD[7,8], which seriously affected the recovery of brain function[9-11]. These factors may result in increased fatality and disability rates, prolonged hospitalization time[12], and increased costs of treatment and rehabilitation[13]. A series of severe health problems caused by PSD is one of the leading potential causes of stroke-related death[14-17]. Once aspiration occurs, aspiration pneumonia and acute airway obstruction can occur, which can directly lead to death in severe cases[18]. Statistics have shown that 20% of stroke patients die of aspiration pneumonia caused by dysphagia within one year of onset[19]. In addition, PSD can also create a social, psychological and economic burden for patients and their families. Some researchers have found that PSD was related to depression, loneliness, anxiety and panic disorders, embarrassment and loss of self-esteem during eating, which significantly reduced the quality of life of patients[20,21].

Corresponding Author: Bolun Zhao, Ph.D; e-mail: zhaobolun@dlu.edu.cn

Thus, PSD is closely associated with poor outcomes in stroke patients. It is evident that all patients with stroke must be evaluated for dysphagia. If PSD is noted, it must be given great attention. Systemic analysis of factors related to the prognosis of PSD to improve strategic interventions and prognosis is indispensable.

Some previous studies[6,26,27,28,29,30,31,36,37,39,41,42,44,47,48,50,51,52] have reported a series of factors related to good or poor outcomes of PSD, including age, time of intervention, malnutrition, severity of stroke and dysphagia, location of the stroke, degree of dysfunction before onset and on admission, and disturbance of consciousness. However, these studies did not provide consistent evidence on any certain factor for medical decision-making and intervention. The conflicting findings could plausibly be attributed to heterogeneous patient populations, small sample sizes lacking statistical power and a lack of convincing and rigorous designs. Most importantly, there are no specific data to compare and rank these prognostic factors, making it difficult to clarify which prognostic factors are the most stable and critical. Therefore, it is urgent to discover important prognostic factors to establish multivariable prognostic prediction models and assessment scales in follow-up studies. To our knowledge, no systematic review involving a meta-analysis of observational studies on the prognostic factors of PSD has been conducted to date. To help clinicians better detect patients at risk and to provide effective interventions for PSD, we conducted a meta-analysis.

Materials and Methods

The search strategy was developed, reviewed and refined following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[22].

Literature Search Strategy

The PubMed, Embase, Web of Science, EBSCO, Cochrane Library, ScienceDirect, Chinese BioMedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), VIP database of Chinese periodicals, and Wanfang Data Knowledge Service Platform databases were searched to identify potentially relevant observational studies. Search terms were set with the subject headings and common terms ("Deglutition Disorders" or "Deglutition Disorder*" or "Swallowing Disorder*" or "Dysphagia") and ("Stroke" or "CVA" or "Cerebrovascular Accident*" or "Brain Vascular Accident*" or "Apoplexy") and ("Prognosis" or "Prognoses" or "outcome*"). The reference lists from the included articles were manually examined to identify other potentially relevant manuscripts. No time or language restrictions were used in the search.

Study Selection

The articles from all the above databases were imported into Endnote, and duplicates were deleted. Articles were screened for potential relevance based on title and abstract, and articles that were clearly outside of the scope of this review were removed. Uncertainty on eligibility was resolved by discussion between the co-authors. After the initial screening, the full texts of the remaining articles were retrieved for the final decision on the inclusion of the studies in the meta-analysis, and discrepancies were resolved by discussion. Studies that meet the following criteria were finally included:

- Case-control and cohort studies that focused on risk factors or predictive factors for the prognosis or outcomes of PSD patients.
- All patients (18 years or older) were diagnosed with poststroke dysphagia.
- Definite standards were used to assess the prognosis or outcomes of PSD patients, which could be variant but acceptable.
- Full-text articles that were published in English or Chinese.
- The studies provided odds ratios (OR) and 95% confidence intervals (CI) values of the prognostic factors that could be used to calculate the statistics.

Data Extraction and Quality Assessment

Two qualified investigators independently extracted and recorded the following information: name of the first author, publication year, study type, characteristics of the participants, sample size, methods of dysphagia assessment, OR value and 95% CI. The methodological quality of the included studies was evaluated using the Newcastle-Ottawa Scale (NOS), which was used for case-control studies and cohort studies, and was based on the following three components: selection, comparability, and exposure (outcome)[23]. The total possible NOS score is 9 points, and 0–3 points, 4–6 points and 7–9 points represent low-, medium- and high-quality, respectively.

Statistical Analysis

Review Manager 5.3 and Stata/SE 15.1 were used to conduct the meta-analysis and assess publication bias, respectively. OR were used for the quantitative analyses. Forest plots were produced to visually assess the OR and corresponding 95% CI for each factor. Chi-square tests were used for hypothesis testing (Z distribution, $p < 0.05$ was considered statistically significant). The I^2 statistic was used to assess each study's heterogeneity size, which was described as low, moderate and high with I^2 values of 25, 50 and 75%, respectively[24]. The random-effects model was chosen when I^2 was > 50%, and the fixed-effects model was chosen when I^2 was ≤ 50%. Sensitivity analysis was performed by removing the articles one by one and then comparing the I^2, OR and *p*-values before and after the removal. Begg's and Egger's regression asymmetry tests were conducted using Stata/SE 15.1 to evaluate possible publication bias; $p < 0.05$ was considered indicative of statistically significant publication bias. Prognostic factors for PSD were estimated using the OR and 95% CI values, and the factor was considered to be significantly associated when the *p*-value was < 0.05.

Results

Characteristics and Quality of the Selected Studies

The search flowchart is shown in Figure 1. A total of 3132 relevant studies were searched (PubMed: n = 518, Embase: n = 342, Web of Science: n = 270, EBSCO: n = 52, Cochrane library: n = 22, Science direct: n = 1327, CNKI: n

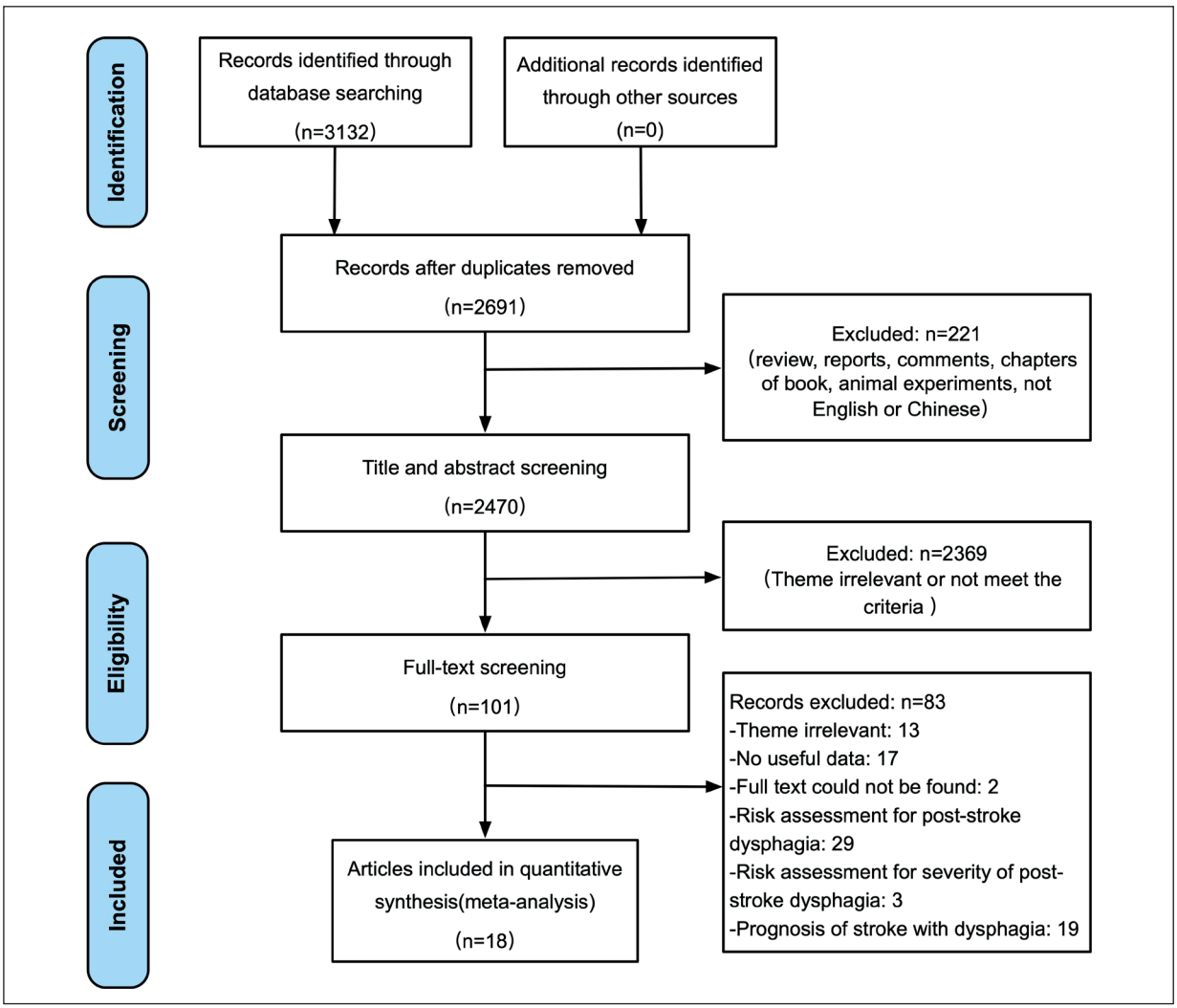

Figure 1. Flowchart of the selection process and reasons for study exclusion.

= 389, CBM: n = 107, VIP: n = 44, WAN FANG DATA: n = 61). Endnote X9 identified 441 duplicate articles; 221 articles were excluded for ineligible publication type or research type. After screening the titles and abstracts, 2369 articles were excluded for uncorrelated research content. After reading the full texts, 18 articles were included from the remaining 101. Among the 18 studies[6,26,27,28,29,30,31,36,37,39,41,42,44,47,48,50,51,52], one study[51] was a case-control study, and 17 studies[6,26,27,28,29,30,31,36,37,39,41,42,44,47,48,50,52] were cohort studies. All the included studies were of high quality (NOS scores ≥ 7 points). The characteristics and quality scores of the included studies are listed in Table I. No publication bias was discovered among the selected studies (Table II).

Prognostic Factors

A total of 28 factors related to the prognosis of PSD were extracted from the included studies. Only 11 of the 28 factors were finally included in the meta-analysis and were identified by three or more studies. The included prognostic factors contained older age, severe stroke, poor performance ability of ADL, malnutrition, early intervention, severe dysphagia, reduced level of consciousness, aspiration, brainstem injury, bihemispheric brain injury, and an MRS (modified Rankin scale) score of 0 before onset.

Older age

Ten included studies[6,26,29,37,39,41,42,47,48,50] reported the impact of older age on the prognosis of PSD. The pooled data under the random-effects model showed an OR of 1.75 (1.50-2.04, $p < 0.00001$) with substantial heterogeneity ($I^2 = 96\%$, $p < 0.00001$). The sensitivity analysis revealed that four studies[26,29,39,42] were possible outliers. By omitting the four aberrant studies, the heterogeneity was sharply reduced ($I^2 = 25\%$, $p = 0.25$), and the synthesized OR was 1.78 (1.45-2.17, $p < 0.00001$) under the fixed-effect model (Figure 2). Older age was a risk factor for poor prognosis of PSD.

Severe stroke

Five included studies[29,30,36,37,44] explored the relationship between the severity of stroke and the prognosis of PSD. The results of the initial meta-analysis showed an OR of 3.06 (1.69-5.53, $p < 0.001$) under the random-effects model, but high heterogeneity was found ($I^2 = 88\%$, $p < 0.00001$). By sensitivity analysis, one study[44] was omitted without a significant effect on the OR of 3.66 (2.195-6.12, $p < 0.00001$) under the random-effects model, and the heterogeneity changed to moderate ($I^2 = 60\%$, $p = 0.25$) (Figure 3). The results showed that the more severe the stroke was, the worse the prognosis of PSD.

Poor ability ADL

Four included studies[6,42,47,48] reported the ability to perform activities of daily life (ADL) to predict the prognosis of PSD. The heterogeneity was moderate ($I^2 = 66\%$, $p = 0.23$). Heterogeneity was not altered by removing any studies, and all studies remained. The results of the meta-analysis showed an OR of 1.75 (0.84-3.63, $p > 0.05$) under the random-effects model (Figure 4). The ability to perform ADL was not significantly related to the prognosis of PSD.

Malnutrition

Four included studies[31,37,42,50,51] were pooled to investigate the effect of malnutrition on the prognosis of PSD. The analysis was conducted under the fixed-effects model with an OR of 1.36 (1.22-1.53, $p < 0.00001$), without apparent heterogeneity ($I^2 = 25\%$, $p = 0.26$) (Figure 5). Malnutrition was a risk factor for poor prognosis of PSD.

Early intervention

Data from four included studies[26,27,28] were input into the meta-analysis, and the pooled OR was 0.75 (0.61-0.93, $p < 0.05$). The heterogeneity changed from high ($I^2 = 96\%$, $p < 0.00001$) to moderate ($I^2 = 73\%$, $p = 0.03$) by omitting one aberrant study. Under the random-effects model, the synthesized OR was 0.54 (0.47-0.88, $p < 0.00001$) (Figure 6). Early intervention was a protective factor for the prognosis of PSD.

Severe dysphagia on admission

Four included studies[27,28,42,51] explored the relationship between the severity of *dysphagia on admission* and the prognosis of PSD. Moderate heterogeneity was observed ($I^2 = 70\%$, $p = 0.02$). The meta-analysis was performed under the random-effects model, and the results of the meta-analysis showed an OR of 1.16 (1.03-1.29, $p < 0.05$) (Figure 7). Severe dysphagia on admission was a risk factor for poor prognosis of PSD.

Aspiration

Three studies[36,37,41] evaluated the impact of aspiration on the prognosis of PSD. No heterogeneity was found ($I^2 = 0\%$, $p = 0.02$). The meta-analysis was performed under the fixed-effects model, and the results of the meta-analysis showed an OR of 7.64 (5.94-9.82, $p < 0.00001$) (Figure 8). Aspiration was a strong risk factor for poor prognosis of PSD.

Table I. Characteristics of the included studies.

Study	Publication (year)	Country	Setting	Study design	Number of participants	Sex (M/F)	Age (years)	Exposure factors[a]	Quality assessment[b]
Nakajima et al[29]	2012	Japan	Hospital	Cohort	512	209/303	82 (Range 75–87)	1,2,6,12,13,28	7★
Nakadate et al[50]	2016	Japan	Rehabilitation Hospital	Cohort	107	64/43	72.1±11.0	1,4,6	7★
Takahata et al[26]	2011	Japan	Hospital	Cohort	219	128/91	69.2±11.7 (Early intervention) 68.0 ± 12.7(Control)	1,5,8,14,15	8★
Ikenaga et al[51]	2017	Japan	Rehabilitation ward	Case-control	72	52/20	72.9±11.4 (Complete oral intake) 78.9±8.3 (Incomplete oral intake)	4,7,8	8★
Shimizu et al[42]	2019	Japan	Rehabilitation Hospital	Cohort	188	120/68	78.9 ± 7.7	1,3,4,7	8★
Toscano et al[44]	2015	Italy	Hospital	Cohort	275	138/137	73± 11.6	2,8,16,27	8★
Nakajima et al[30]	2012	Japan	Hospital	Cohort	525	322/203	69.9 ± 11.6(Oral intake) 77.1 ± 9.2 (Non-oral intake)	2,3,28	7★
Calvo et al[41]	2019	Italy	Rehabilitation Hospital	Cohort	163	78/85	75.8±10. 9	1,9,17	9★
Kumar et al[36]	2014	USA	Hospital	Cohort	323	134/189	75.9 ±13.6	2,9,10,11,18	8★
Nishioka et al[31]	2017	Japan	Hospital	Cohort	264	165/109	78.5 ±7.5	3,4,5,19	8★
Zhang et al[48]	2012	China	Hospital	Cohort	179	121/58	67.47±9.8	1,3,13	8★
Zhan et al[39]	2018	China	Rehabilitation ward	Cohort	97	97/73	Range 35-91	1,8,14,18	8★
Lan et al[47]	2002	China	Hospital	Cohort	56	30/26	69.3 (Range 36-85)	1,3,14,18	8★
Wang et al[6]	2011	China	Hospital	Cohort	116	67/49	72 (Range 45-85)	1,3	9★
Peng et al[28]	2006	China	Hospital	Cohort	84	39/45	61.4 (Range 33-85)	5,7,8,20	9★
Wei et al[52]	2010	China	Hospital	Cohort	118	89/29	68.09±7.85	8,21,22,23,24,25,26	8★
Xie et al[37]	2015	China	Hospital	Cohort	296	149/150	64.3±11.2 (no dysphagia) 75.6±6.5 (dysphagia)	1,2,4,5,9,11	7★
Hu et al[27]	2013	China	Hospital	Cohort	80	36/34	72.5 (Range 56-88)	5,8,7,20	8★

[a]Exposure factors: 1. older age; 2. severity of stroke; 3. poor ADL performance; 4. malnutrition; 5. early intervention; 6. elevated WBCs; 7. severe dysphagia on admission; 8. reduced level of consciousness; 9. aspiration; 10. dysarthria; 11. intubation; 12. cardioembolism; 13. hyperlipidaemia; 14. brainstem injury; 15. haematoma volume; 16. severity of white matter changes; 17. presence of residue; 18. bihemispheric injury; 19. pneumonia incidence; 20. visual and auditory impairments; 21. lingual hemiplegia; 22. difficulty in lifting the tongue; 23. bilateral facial paralysis; 24. decreased autonomic cough; 25. disappearance of pharyngeal reflex; 26. sound changes after eating; 27. haemorrhagic stroke; 28. An MRS score of 0 before onset

[b]The quality assessment was performed using the NOS scale.

Table II. Odds ratios with 95% confidence interval values and publication bias of risk factors for the included studies.

Relative factors	Combination studies	Analysis model	Hetero-geneity of studies (I^2)	Meta-analysis		Begg's test (*p*)	Egger's test (*p*)
				OR (95% CI)	*p*-value		
Older age	6	Fixed	25%	1.78(1.45, 2.17)	$p<0.00001$	0.851	0.230
Severe stroke	4	Random	60%	3.66(2.19, 6.12)	$p<0.00001$	0.734	0.92
Poor performance ability of ADL	4	Random	66%	1.75(0.84, 3.63)	$p=0.14$	1.000	0.072
Malnutrition	5	Fixed	25%	1.36(1.22, 1.53)	$p<0.00001$	0.086	0.162
Early intervention	3	Random	73%	0.64(0.47, 0.88)	$p=0.005$	0.296	0.118
Severe dysphagia on admission	4	Random	70%	1.16(1.03, 1.29)	$p=0.01$	0.089	0.156
Aspiration	3	Fixed	0%	7.64(5.94, 9.82)	$p<0.00001$	0.602	0.066
Reduced level of consciousness	4	Random	72%	1.03(1.00, 1.07)	$p=0.03$	0.174	0.142
Brainstem injury	3	Fixed	0%	4.82(3.01, 7.72)	$p<0.00001$	0.602	0.309
Bihemispheric injury	3	Random	57%	3.00(1.67, 5.40)	$p=0.0002$	1.000	0.262
An MRS score of 0 before onset	3	Fixed	0%	0.58(0.47, 0.71)	$p<0.00001$	0.296	0.053

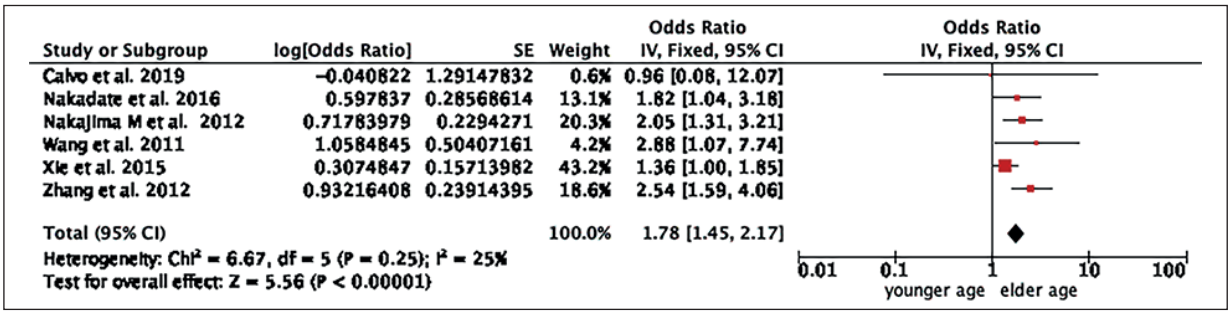

Figure 2. Forest plot for older age.

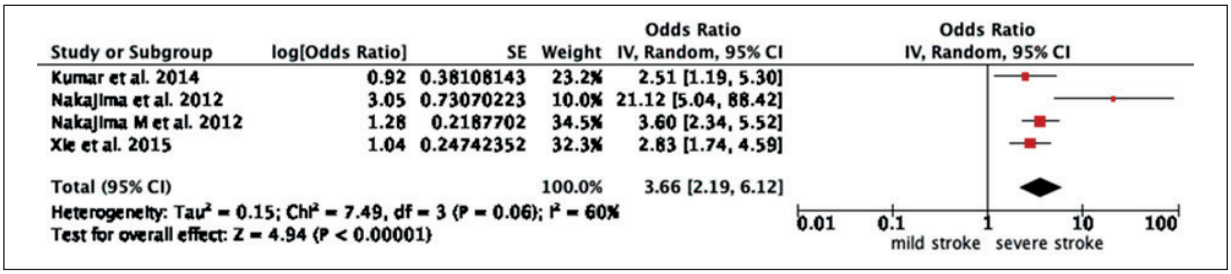

Figure 3. Forest plot for the severity of stroke.

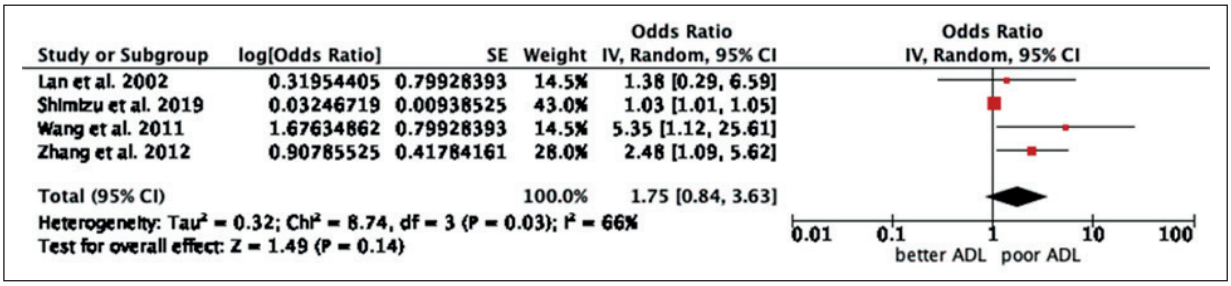

Figure 4. Forest plot for the performance ability of ADL.

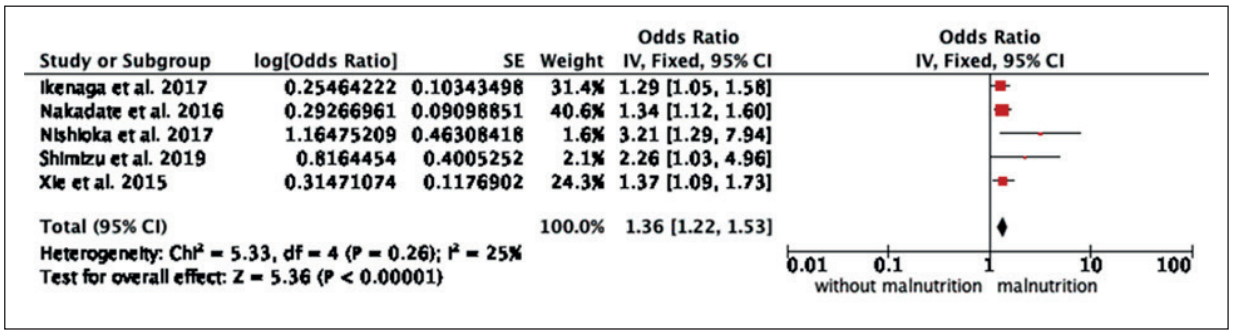

Figure 5. Forest plot for malnutrition.

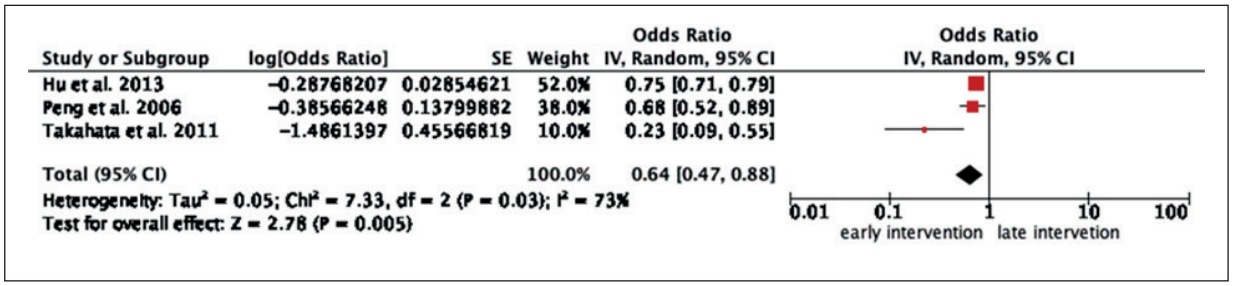

Figure 6. Forest plot for early intervention.

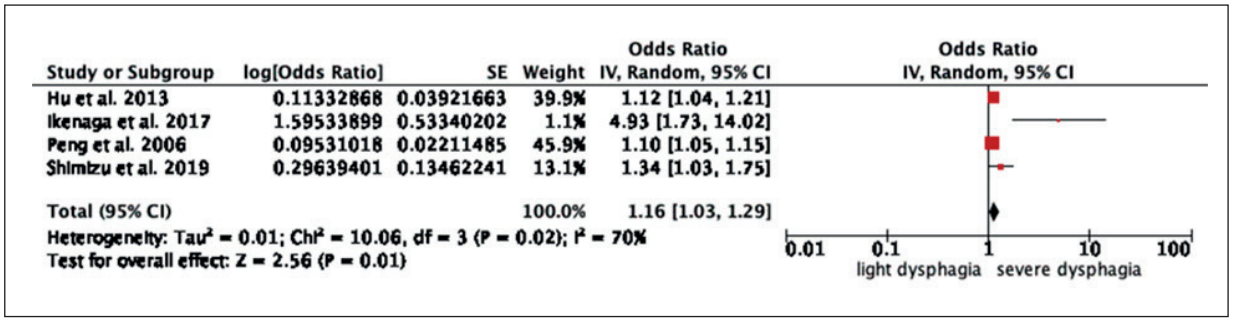

Figure 7. Forest plot for the severity of dysphagia on admission.

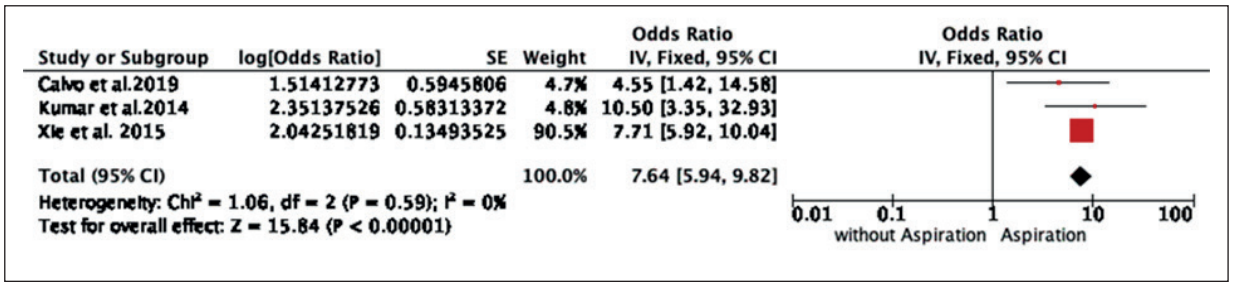

Figure 8. Forest plot for aspiration.

Reduced level of consciousness

Seven included studies[26,27,28,29,44,51,52] reported that a reduced level of consciousness was related to the prognosis of PSD. The heterogeneity was high ($I^2 = 93\%$, $p < 0.00001$). Through the sensitivity analysis, three aberrant studies[26,29,52] were found and omitted, and the analysis under the random-effects model showed a similar result with an OR of 1.03 (1.00-1.07, $p < 0.05$) (Figure 9). A reduced level of consciousness was a risk factor for poor prognosis of PSD.

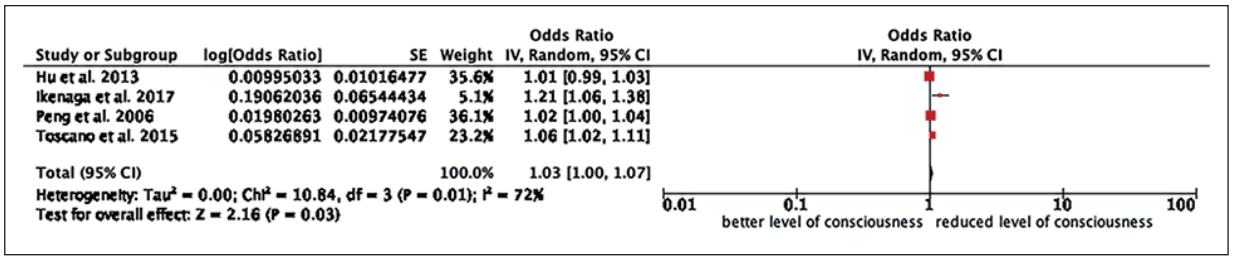

Figure 9. Forest plot for the reduced level of consciousness.

Brainstem injury

Three included studies[26,39,47] reported that patients with brainstem injury presented a close association with poor prognosis of PSD. No heterogeneity was found ($I^2 = 0\%$, $p = 0.80$) among the studies. The meta-analysis was performed under the fixed-effects model, and the results showed that brainstem injury had a significantly higher association with poor prognosis of PSD (OR 4.82; 3.01-7.72, $p < 0.00001$) (Figure 10).

Bihemispheric injury

Data from three included studies[36,39,47] were pooled to investigate the effect of bihemispheric injury on the prognosis of PSD. Moderate heterogeneity was found ($I^2 = 57\%$, $p = 0.10$). Under the random-effects model, the results of the meta-analysis showed an OR of 3.0 (1.67-5.40, $p < 0.001$) (Figure 11). Bihemispheric injury was a risk factor that was significantly associated with the poor prognosis of PSD.

MRS score of 0 before onset

Data on the influences of general status before onset on the prognosis of PSD were available from three studies[29,30,31], with a pooled OR of 0.58 (0.47-0.71, $p < 0.00001$) under the fixed-effects model with no between-study heterogeneity ($I^2 = 0\%$, $p = 0.54$) (Figure 12). An MRS score of 0 before onset was regarded as a protective factor for better prognosis of PSD.

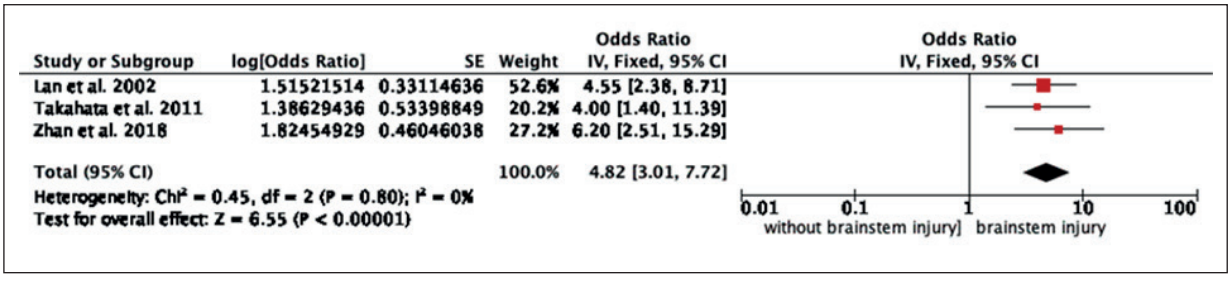

Figure 10. Forest plot for brainstem injury.

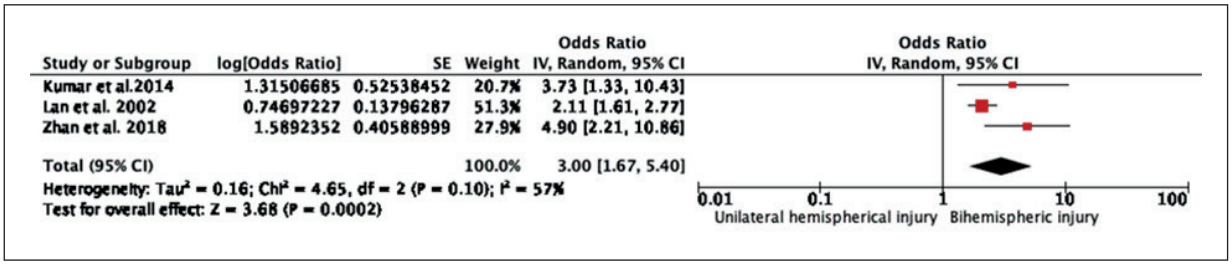

Figure 11. Forest plot for bihemispheric injury.

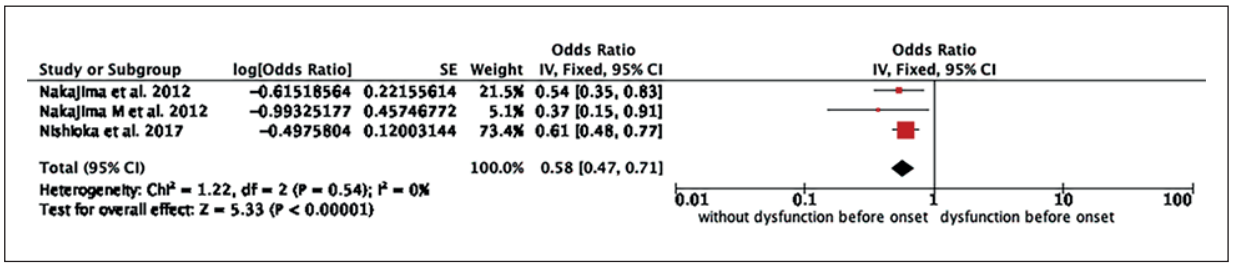

Figure 12. Forest plot for an MRS score of 0 before onset.

Discussion

PSD has gained increased attention in recent years due to its high prevalence, persistence, and implications on the health, quality of life, and recovery of stroke survivors. Swallowing function is one of the first functions to recover for PSD patients[25]. Identifying which factors are related to the outcomes of PSD is critical to better identify patients at risk of poorer outcomes and is also essential for predicting the probability of recovering oral feeding or continuing enteral tube feeding over a long period of time and effectively developing rehabilitation strategies. In this study, we conducted a meta-analysis to identify the factors associated with the prognosis of PSD. Ten factors were found to be significantly related to the prognosis of PSD, including older age, severe stroke, poor performance ability of ADL, malnutrition, early intervention, severe dysphagia, reduced level of consciousness, aspiration, brainstem injury, bihemispheric brain injury and an MRS score of 0 before onset. Poor performance ability of ADL did not show good predictive value.

Early intervention and an MRS score of 0 before onset were two protective factors identified in this meta-analysis. Early intervention in dysphagia was an active protective factor for the prognosis of PSD. The earlier the intervention begins, the better the recovery of dysphagia[26-28]. Early screenings for dysphagia should be performed within 24 hours after stroke onset to formulate and employ effective rehabilitation and treatment measures as soon as possible, which could promote a positive outcome for the functional recovery of PSD. An MRS score of 0 was used in the included studies to reflect a patient's good general status[29-31]. An MRS score of 0 before onset showed a moderate association with a better prognosis of PSD. The results showed that patients in good general status before the onset of stroke had a higher incidence of regaining swallowing function than those who already had a certain degree of disability.

The presence of aspiration was the strongest predictor of prolonged dysphagia, with a pooled OR of 7.64. Overt clinical signs of aspiration were related to severe dysphagia in patients with stroke and were associated with a series of complications. In Wilmskoetter et al[32], the results also showed that the absence of aspiration was the strongest predictor for gastrostomy tube removal in patients with dysphagia after stroke. Ickenstein[33] reached a similar conclusion that signs of aspiration in the first 72 hours of acute stroke can predict severe swallowing problems on Day 90. Therefore, PSD patients should be evaluated with established dysphagia scales or instruments to prevent aspiration pneumonia and malnutrition and to reduce the further aggravation of dysphagia caused by aspiration.

Severe stroke, brain stem and bihemispheric injury were identified as strong risk factors for poor prognosis of PSD in this meta-analysis. As a powerful prognostic factor for dysphagia[14,34,35], stroke severity was recognized as a significant predictor for stroke recovery[29,30,36,37]. The National Institutes of Health Stroke Scales (NIHSS) score is a popular tool for evaluating the severity of stroke. The results of our meta-analysis showed that a higher NIHSS score was strongly associated with poor outcomes of PSD. However, stroke symptoms fluctuate dramatically in the acute phase of stroke[38], and the evaluation time of the NIHSS score has a significant impact on the predictive effect. Thus, the NIHSS score on Day 10[29,30] was more predictive of the long-term outcome of the swallowing status of PSD patients than the NIHSS score on admission. Brain stem and bihemispheric injury[36,39,40] emerged as substantial negative predictive factors for the prognosis of PSD, with pooled ORs of 4.82 and 3.00, respectively. Lesions involving the brainstem where the medulla oblongata is located, or bilateral cortical brainstem tracts caused by stroke, are the main mechanisms of PSD[41]. The primary motor cortex associated with swallowing

is involved, particularly for larger lesions such as bihemispheric injuries, and PSD is more likely to persist. Therefore, more attention should be given to PSD patients with brain stem and bihemispheric injury for better planning rehabilitation and health care strategies.

Older age and malnutrition were moderate risk factors for the prognosis of PSD. Based on the results of the meta-analysis, we found that an age ≥ 70 years old was moderately associated with poor outcomes of PSD, which was a negative predictor of oral feeding resumption[42]. With increasing age, the volume and contractile intensity of the oral, facial and pharyngeal muscles decrease significantly. These factors affected the initiation and coordination of swallowing function, and other chronic diseases often influence patients with advanced age and obtaining their participation in the therapy and rehabilitation process was difficult. All the above shortcomings of older age were reasons for the poor prognosis of PSD. However, the average ages of the participants in the included studies of this meta-analysis were all over 60 years, which made the association effect not strong. However, it suggested that an increase in age would further exacerbate the prognosis of PSD. Malnutrition was moderately associated with poor outcomes of PSD. Dysphagia after stroke leads to malnutrition owing to insufficient nutritional intake and causes secondary sarcopenia of the swallowing-related muscles, which results in prolonged dysphagia and reduced effects of swallowing rehabilitation[43]. PSD patients with malnutrition tend to have a higher incidence rate of pneumonia, which negatively affects swallowing function[31]. Thus, undergoing aggressive nutritional support in conjunction with swallowing rehabilitation is beneficial for PSD patients to recover from dysphagia.

Severe dysphagia on admission and reduced level of consciousness were identified as minor risk factors for the prognosis of PSD. The severity of dysphagia was closely related to the type and characteristics of stroke, which determined the paralysis degree of the muscles related to swallowing. Some patients with severe dysphagia still needed nasogastric feeding to maintain nutrition after various rehabilitation training. In addition, stroke patients with severe dysphagia on admission demonstrated more severe malnutrition[43,44], which was another negative predictor for poor prognosis of PSD, as discussed above. Therefore, the patients with severe dysphagia on admission were more likely to have poor outcomes of dysphagia. A reduced level of consciousness emerged as a minor association with the poor prognosis of PSD, with a pooled OR of 1.03. Previous studies[45-47] have reported that cognitive impairment caused by stroke-related brain lesions might impair swallowing function. Moreover, patients with a reduced level of consciousness have a poor ability to judge food information and poor cooperation ability, which seriously affects the therapeutic and rehabilitative effects. Therefore, the rehabilitation of cognitive impairment is also an essential basis for the recovery of PSD.

In addition, this meta-analysis did not find any significant associations between poor performance ability of ADL and prognosis of PSD, although poor performance ability of ADL is a risk factor that affected the prognosis of PSD in many studies in the literature[43,48-50]. The contradictory conclusion may be caused primarily by interaction effects between poor performance ability of ADL and other risk factors poststroke. One recently published review showed that age, impaired cognitive function and impaired motor function of the leg were associated with a decline in ADL poststroke[51]. Furthermore, there could have been selection bias owing to most of the PSD study population being from hospitals, where PSD patients are more likely to have a history of poor performance ability of ADL.

This meta-analysis aimed to better identify the factors related to the prognosis of PSD, including protective factors and risk factors, which serve as helpful, simple and convenient resources for preparing rehabilitation plans, making a judgement of when a patient may experience recovery of oral intake and when considering a gastrostomy. Especially in some cases, equipment examinations such as a VFSS (videofluoroscopic swallowing study) or a FEES (fibreoptic endoscopic evaluation of swallowing) cannot be performed due to professional and environmental limitations. To date, no other meta-analysis has been found that covers this topic. We hope our results may provide insight into the prediction of prognosis for dysphagia after stroke.

Limitations

There are several limitations to this meta-analysis. First, 28 factors were extracted from 18 included studies, but only 11 of the 28 factors were identified simultaneously by more than three studies that met the criteria for inclusion in the meta-analysis. Some factors, such as hyperlipidaemia, haemor-

rhagic stroke, and decreased autonomic cough, which were reported as significant risk factors for the prognosis of PSD by only one or two studies, were excluded by the authors. Second, with regard to outcome assessment, recovery to complete oral intake was used as the outcome indicator in 3 of the 18 included studies, and standardized screening tools for dysphagia were chosen to evaluate the prognosis of PSD in the other 15 studies. Subgroup analysis was unable to be performed for the factors that were included in fewer studies. Although the inconsistencies in the evaluation of the outcome indicators between the studies did not affect the overall results, the results of the meta-analysis should be interpreted with caution. Third, Begg's and Egger's tests were performed to calculate publication bias for all relative factors included in this meta-analysis, and no significant bias was found. However, publication bias could not be fully excluded because fewer studies lowered the statistical power of Begg's and Egger's tests. Last, the literature finally included in this study was mainly published in Chinese, which could also result in some bias in our study. Therefore, more high-quality studies are needed to provide sufficient evidence for further meta-analysis.

Conclusions

Previous studies have identified multiple related factors for the prognosis of PSD. In this study, ten factors were finally identified as critical prognostic factors that are significantly associated with the prognosis of PSD. The critical prognostic factors identified in this meta-analysis may serve as helpful references for clinical decision-making during the rehabilitation process of PSD patients and might be an important support for the establishment of a prognostic prediction tool for PSD.

Conflict of Interests

The authors declare that they have no conflict of interests.

Funding

This study was funded by the Dalian Science and technology innovation fund program (No. 2020JJ27SN074).

Acknowledgements

The authors would like to thank the Stroke Rehabilitation Research Team in the Nursing School, Second Military Medical University, China for their support in the literature search and quality analysis.

References

1) Martino R, Foley N, Bhogal S, Diamant N, Speechley M, Teasell R. Dysphagia after stroke: incidence, diagnosis, and pulmonary complications. Stroke 2005; 36: 2756-2763.
2) Takizawa C, Gemmell E, Kenworthy J, Speyer R. A Systematic Review of the Prevalence of Oropharyngeal Dysphagia in Stroke, Parkinson's Disease, Alzheimer's Disease, Head Injury, and Pneumonia. Dysphagia 2016; 31: 434-441.
3) Wu WJ, Bi X, Song L, Liu ZH, Zhang JM, Huang Q. Value of applying water swallowing test for patients with dysphagia after acute stroke. J ShangHai JiaoTong Uiversity (Medical Science) 2016; 36: 1049-1053.
4) Sun WP, AYiGuLi AS, Wang XH, Huang YN. Standardized Swallowing Assessment of Acute Stroke Patients: an Analysis of 115 Cases. Chin J Rehabil Theory Pract 2006; 12: 282-284.
5) Chinese expert group on dysphagia and nutrition management in stroke patients. Chinese expert consensus on the swallowing disorder nutritional management of stroke patient (2013). Chin J Stroke 2013; 8: 973-983.
6) Wang XM, Zhu C, Li W, Li GZ, Wang Y, Lin W, Yang L, Hou Y. Analysis of prognosis factors of for swallowing disorder of patients with stroke. Shandong Medical Journal 2011; 51: 68-69.
7) Geeganage C, Beavan J, Ellender S, Bath PM. Interventions for dysphagia and nutritional support in acute and subacute stroke. Cochrane Database Syst Rev 2012; 10: Cd000323.
8) Joundi RA, Martino R, Saposnik G, Giannakeas V, Fang J, Kapral MK. Predictors and Outcomes of Dysphagia Screening After Acute Ischemic Stroke. Stroke 2017; 48 :900-906.
9) Smith CJ, Kishore AK, Vail A, Chamorro A, Garau J, Hopkins SJ, Di Napoli M, Kalra L, Langhorne P, Montaner J, Roffe C, Rudd AG, Tyrrell PJ, van de Beek D, Woodhead M, Meisel A. Diagnosis of Stroke-Associated Pneumonia: Recommendations From the Pneumonia in Stroke Consensus Group. Stroke 2015; 46: 2335-2340.
10) Ebihara S, Sekiya H, Miyagi M, Ebihara T, Okazaki T. Dysphagia, dystussia, and aspiration pneumonia in elderly people. J Thorac Dis 2016; 8: 632-639.
11) Al-Khaled M, Matthis C, Binder A, Mudter J, Schattschneider J, Pulkowski U, Strohmaier T, Niehoff T, Zybur R, Eggers J, Valdueza JM, Royl G; for QugSS II Group. Dysphagia in Patients with Acute Ischemic Stroke: Early Dysphagia Screening May Reduce Stroke-Related Pneumonia and Improve Stroke Outcomes. Cerebrovasc Dis 2016; 42: 81-89.
12) Altman KW, Schaefer SD, Yu GP, Hertegard S, Lundy DS, Blumin JH, Maronian NC, Heman-Ackah YD, Abitbol J, Casiano RR; Neurolaryngology Subcommittee of the American Academy of Otolaryngology-Head and Neck Surgery. The voice and laryngeal dysfunction in stroke: a report from the Neurolaryngology Subcommittee of

the American Academy of Otolaryngology-Head and Neck Surgery. Otolaryngol Head Neck Surg 2007; 136: 873-881.

13) Melgaard D, Rodrigo-Domingo M, Mørch MM. The Prevalence of Oropharyngeal Dysphagia in Acute Geriatric Patients. Geriatrics (Basel) 2018; 3: 15.
14) Henke C, Foerch C, Lapa S. Early Screening Parameters for Dysphagia in Acute Ischemic Stroke. Cerebrovasc Dis 2017; 44: 285-290.
15) Poisson P, Laffond T, Campos S, Dupuis V, Bourdel-Marchasson I. Relationships between oral health, dysphagia and undernutrition in hospitalised elderly patients. Gerodontology 2016; 33: 161-168.
16) Cabré M, Serra-Prat M, Force L, Almirall J, Palomera E, Clavé P. Oropharyngeal dysphagia is a risk factor for readmission for pneumonia in the very elderly persons: observational prospective study. J Gerontol A Biol Sci Med Sci 2014; 69: 330-337.
17) Chen LQ, Zhang QD, Pan SY, Zhou CL, Tan MQ, Cheng DH , Zhang XM. Current status of prevention of aspiration in stroke patients. Nurs Practic and Res 2016; 13: 27-30.
18) Carucci LR, Turner MA. Dysphagia revisited: common and unusual causes. Radiographics 2015; 35: 105-122.
19) Wilkins T, Gillies RA, Thomas AM, Wagner PJ. The prevalence of dysphagia in primary care patients: a HamesNet Research Network study. J Am Board Fam Med 2007; 20: 144-150.
20) Holland G, Jayasekeran V, Pendleton N, Horan M, Jones M, Hamdy S. Prevalence and symptom profiling of oropharyngeal dysphagia in a community dwelling of an elderly population: a self-reporting questionnaire survey. Dis Esophagus 2011; 24: 476-480.
21) Ekberg O, Hamdy S, Woisard V, Wuttge-Hannig A, Ortega P. Social and psychological burden of dysphagia: its impact on diagnosis and treatment. Dysphagia 2002; 17: 139-146.
22) Moher D, Liberati A, Tetzlaff J, Altman D G. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009; 339: b2535.
23) Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-Analyses. 2011. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm.
24) Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-560.
25) Oto T, Kandori Y, Ohta T, Domen K, Koyama T. Predicting the chance of weaning dysphagic stroke patients from enteral nutrition: a multivariate logistic modelling study. Eur J Phys Rehabil Med 2009; 45: 355-362.
26) Takahata H, Tsutsumi K, Baba H, Nagata I, Yonekura M. Early intervention to promote oral feeding in patients with intracerebral hemorrhage: a retrospective cohort study. BMC Neurol 2011; 11: 6.
27) Hu XQ, Li M, Zhang CX. Analysis of factors influencing rehabilitation of stroke patients with dysphagia. Guide of Chin Med 2013; 11: 493-494.
28) Peng HS, Yuan CL. Influence factors of rehabilitation therapy of dysphagia following stroke. Chin J Rehabil Med 2006; 21: 142-144.
29) Nakajima M, Inatomi Y, Yonehara T, Hashimoto Y, Hirano T. Acquisition of oral intake in severely dysphagic patients with acute stroke: a single-center, observational study involving a database of 4972 consecutive stroke patients. J Neurol Sci 2012; 323: 56-60.
30) Nakajima M, Inatomi Y, Yonehara T, Hashimoto Y, Hirano T, Uchino M. Oral intake 6 months after acute ischemic stroke. Intern Med 2012; 51: 45-50.
31) Nishioka S, Okamoto T, Takayama M, Urushihara M, Watanabe M, Kiriya Y, Shintani K, Nakagomi H, Kageyama N. Malnutrition risk predicts recovery of full oral intake among older adult stroke patients undergoing enteral nutrition: Secondary analysis of a multicentre survey (the APPLE study). Clin Nutr 2017; 36: 1089-1096.
32) Wilmskoetter J, Herbert TL, Bonilha HS. Factors Associated With Gastrostomy Tube Removal in Patients With Dysphagia After Stroke: A Review of the Literature. Nutr Clin Pract 2017; 32: 166-174.
33) Ickenstein GW, Höhlig C, Prosiegel M, Koch H, Dziewas R, Bodechtel U, Müller R, Reichmann H, Riecker A. Prediction of outcome in neurogenic oropharyngeal dysphagia within 72 hours of acute stroke. J Stroke Cerebrovasc Dis 2012; 21: 569-576.
34) Beharry A, Michel P, Faouzi M, Kuntzer T, Schweizer V, Diserens K. Predictive Factors of Swallowing Disorders and Bronchopneumonia in Acute Ischemic Stroke. J Stroke Cerebrovasc Dis 2019; 28: 2148-2154.
35) Fernández-Pombo A, Seijo-Raposo IM, López-Osorio N, Cantón-Blanco A, González-Rodríguez M, Arias-Rivas S, Rodríguez-Yáñez M, Santamaría-Nieto A, Díaz-Ortega C, Gómez-Vázquez E, Martínez-Olmos MÁ. Lesion location and other predictive factors of dysphagia and its complications in acute stroke. Clin Nutr ESPEN 2019; 33: 178-182.
36) Kumar S, Doughty C, Doros G, Selim M, Lahoti S, Gokhale S, Schlaug G. Recovery of swallowing after dysphagic stroke: an analysis of prognostic factors. J Stroke Cerebrovasc Dis 2014; 23: 56-62.
37) Xie JX, Niu JX, Zhang HY, Wang WP, Bu HW, Li SH. Factors Related with Outcome of Dysphagia after Stroke. Chin J Rehabil Theory Practic 2015; 21: 1352-1355.
38) Ferrari J, Knoflach M, Kiechl S, Willeit J, Schnabl S, Seyfang L, Lang W; Austrian Stroke Unit Registry Collaborators. Early clinical worsening in patients with TIA or minor stroke: the Austrian Stroke Unit Registry. Neurology 2010; 74: 136-141.
39) Zhan ZT, Jiang YJ. Multiple Factors Analysis on the Prognosis of Dysphagia After Stroke. Chin Health Standard Manag 2018; 9: 78-80.

40) Daniels SK, Pathak S, Mukhi SV, Stach CB, Morgan RO, Anderson JA. The Relationship Between Lesion Localization and Dysphagia in Acute Stroke. Dysphagia 2017; 32: 777-784.

41) Calvo I, Pizzorni N, Gilardone G, Mayer F, Vanacore N, Buraschi V, Gilardone M, Corbo M. Predictors of Oral Feeding Resumption after Stroke in a Rehabilitation Hospital: A Retrospective Study. J Stroke Cerebrovasc Dis 2019; 28: 1958-1970.

42) Shimizu A, Maeda K, Koyanagi Y, Kayashita J, Fujishima I, Mori N. The Global Leadership Initiative on Malnutrition-Defined Malnutrition Predicts Prognosis in Persons With Stroke-Related Dysphagia. J Am Med Dir Assoc 2019; 20: 1628-1633.

43) Wakabayashi H, Matsushima M, Uwano R, Watanabe N, Oritsu H, Shimizu Y. Skeletal muscle mass is associated with severe dysphagia in cancer patients. J Cachexia Sarcopenia Muscle 2015; 6: 351-357.

44) Toscano M, Cecconi E, Capiluppi E, Viganò A, Bertora P, Campiglio L, Mariani C, Petolicchio B, Sasso D'Elia T, Verzina A, Vicenzini E, Fiorelli M, Cislaghi G, Di Piero V. Neuroanatomical, Clinical and Cognitive Correlates of Post-Stroke Dysphagia. Eur Neurol 2015; 74: 171-177.

45) Ertekin C, Aydogdu I, Tarlaci S, Turman AB, Kiylioglu N. Mechanisms of dysphagia in suprabulbar palsy with lacunar infarct. Stroke 2000; 31: 1370-1376.

46) Jo SY, Hwang JW, Pyun SB. Relationship Between Cognitive Function and Dysphagia After Stroke. Ann Rehabil Med 2017; 41: 564-572.

47) Lan Y, Huang DF, Chen SZ, Xu GQ, Liu P. Analysis of the prognostic factors of post-stroke dysphagia. Chin J Phys Med Rehabi 2002; 24: 660-662.

48) Zhang YH. Analysis of the ralated Factors influencing dysphagia prognosis after acute stroke. J Neurosci and Ment Health 2012; 12: 338-340.

49) Wondergem R, Pisters MF, Wouters EJ, Olthof N, de Bie RA, Visser-Meily JM, Veenhof C. The Course of Activities in Daily Living: Who Is at Risk for Decline after First Ever Stroke? Cerebrovasc Dis 2017; 43: 1-8.

50) Nakadate A, Otaka Y, Kondo K, Yamamoto R, Matsuura D, Honaga K, Muraoka K, Akaboshi K, Liu M. Age, Body Mass Index, and White Blood Cell Count Predict the Resumption of Oral Intake in Subacute Stroke Patients. J Stroke Cerebrovasc Dis 2016; 25: 2801-2808.

51) Ikenaga Y, Nakayama S, Taniguchi H, Ohori I, Komatsu N, Nishimura H, Katsuki Y. Factors Predicting Recovery of Oral Intake in Stroke Survivors with Dysphagia in a Convalescent Rehabilitation Ward. J Stroke Cerebrovasc Dis 2017; 26: 1013-1019.

52) Wei YL, Liu ZL, Duan XQ. Analysis on prognostic factors on dysphagia patients in stroke unit. Chinese Journal of Rehabilitation Medicine 2010; 25: 322-325.