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# A Significant Association of Malnutrition with Dysphagia in Acute Patients

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## Introduction

Globally, the number of persons aged 60 and above is expected to more than double by 2050, increasing from 901 million in 2015 to 2.1 billion in 2050 [1]. This phenomenon, known as population aging, is occurring throughout the world and has already made elderly dysphagia a subject with considerable impact both from the epidemiological and the individual patient perspective [2]. Elderly dysphagia not only carries the possibility of fatal aspiration pneumonia but also undermines the patient's quality of life. Despite the widespread concerns over elderly dysphagia, the majority of its contributing factors remain to be elucidated, except for stroke as one of the most common causes of dysphagia [3]. Clinically it is well known that aging causes dysphagia; however, analysis of other factors that can cause dysphagia has advanced in recent years.

Malnutrition is originally reported to be the leading cause of the disease burden in developing countries with high morbidity and mortality rates. However, nowadays malnutrition is becoming a novel threat for the elderly in the currently developed

countries [4]. Malnutrition is an independent risk factor causing serious complications and increasing mortality, length of hospital stay, and costs [5]. Dysphagia and malnutrition are apparently associated. Several studies have focused on dysphagia as a prevalent risk factor for malnutrition during recent years [6, 7]. On the other hand, recently Japanese researchers pointed out the importance of malnutrition as an independent risk for dysphagia [8]. The reason why little research in detail has been reported until very recently is that both dysphagia and malnutrition are frequently overlooked conditions despite actual high incidences [9]. Furthermore, little is known about dysphagia in elderly patients with acute diseases compared to those with chronic diseases [6].

Videofluorography (VF) is considered to be the gold standard for evaluation and management of dysphagia [10-12]. In several previous studies concerning the relationship between dysphagia and malnutrition, dysphagia was diagnosed using questionnaires [13,14], and almost no studies have used VF in order to diagnose dysphagia accurately. Even in the case of VF conducted in nutrition research, objective numerical evaluation scales such as the penetration-aspiration scale (PAS) have not

necessarily been fully utilized. PAS was widely used from the beginning to recent years and established in evaluating VF findings [15] in patients of all ages and diseases such as stroke [16], amyotrophic lateral sclerosis [17], Parkinson disease [18], chronic obstructive pulmonary disease (COPD) [19], and head and neck cancer [20]. The Geriatric Nutritional Risk Index (GNRI) [21-23] was adopted recently to replace numerous previously created nutritional measures because of its well-established reliability and ease of calculation, using an objective rather than subjective measurements to determine nutritional risk in hospitalized patient populations.

We hypothesized that clinically high-risk dysphagia in acute patients is significantly associated with malnutrition. In order to prove this hypothesis, we conducted a retrospective study of consecutive acute patients in whom the severity of dysphagia was evaluated numerically by PAS and the nutritional status was quantified by GNRI. By examining the statistical relevance between these numerical evaluations, we thought that the relationship between swallowing dysfunction and nutritional status could be clarified.

## Methods

The entire study protocol was approved by the ethical review board of Asahikawa Medical University, and all patients gave their written informed consent for the present study.

### Patient enrollment

We conducted a retrospective review of the medical records of 165 consecutive patients admitted to Asahikawa Medical University Hospital for acute diseases who underwent VF on suspicion of dysphagia in the year of 2016. According to the diagnosis of acute disease directly responsible for the admission, we classified all enrolled patients into eight categories of disease: brain tumors, cardiovascular diseases, malignancies, musculoskeletal disorders, neurological disorders, pneumonia, stroke, and other diseases. All subjects were capable of oral ingestion before hospitalization, and no patient was dependent on tube feeding or intravenous nutrition.

### Definition of the variables

We set baseline characteristics including representative cardiovascular risk factors and respiratory diseases that might relate to the swallowing dysfunction as variables in multiple logistic regression analysis. Hypertension was defined as a systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg in subjects who were not taking antihypertensive medications or were continuously receiving antihypertensive treatment on an outpatient basis. Diabetes mellitus was defined as a Japan Diabetes Society (JDS) HbA1c value of ≥6.1 [corresponds approximately to the National Glycohemoglobin Standardization Program (NGSP) HbA1c value of ≥6.5] or any continuous antidiabetic treatment on an outpatient basis. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) level of <60 ml/min/1.73 $m^2$ and/or overt albuminuria continuing longer than three months. Congestive heart failure was defined as that previously diagnosed by a cardiovascular specialist. Chronic obstructive pulmonary disease (COPD) was defined as FEV1% (forced expiratory volume in 1 second percentage) of <70% measured with spirometry.

**Baseline nutritional assessment**

All subjects were weighed on a validated weight scale recalibrated every year within 3 days before the date of VF. Body height was measured within 3 months before the date of VF. We calculated the body mass index (BMI; $kg/m^2$) from actual body weight and body height as ideal body weight (IBW). Subjects were fasted from 9:00 PM, blood was taken at 8:00 AM the next morning, and the serum albumin concentration was quickly measured. Serum albumin was measured by standard laboratory techniques with the use of an automatic analyzer within 3 days before the date of VF.

The GNRI formula we used in this study was:

GNRI = [1.489 × albumin (g/L)] + [41.7 × (actual body weight/ideal body weight)]

When actual body weight exceeded ideal body weight, a score of 1 was assigned for the actual body weight/ideal body weight ratio. Although originally the ideal body weight was calculated from the Lorenz formula for GNRI, no difference has been reported between with the use of the Lorenz formula and a BMI of 22.0 $kg/m^2$ for the ideal body weight [24]. The GNRI cutoff value to identify malnourished patients that we adopted in the present study was <91.2 [24,25]. We also used BMI <18.5 [26] and serum albumin <35 g/l as classical criteria of malnutrition for comparison [27].

**Assessment of VF**

Because our hospital is an acute-care hospital, VF was performed as soon as patients suspected of dysphagia were able to tolerate VF. As a result, VF was performed on the 14th day, as a median value, when calculated using the number of days after hospitalization in medical patients and the number of days after surgery in surgical patients. Trained speech-language-hearing therapists (K.H., H.N., and F.Y.) performed the VF assessments using a standard protocol [28-30]. A videorecording of the oral cavity and pharynx was obtained in the lateral plane while the patient swallowed. Loads were 3 ml of thickened barium water, 5 ml of thickened barium water, 3 ml of barium water, 5 ml of barium water, and the barium jelly. The barium solution in water (50% weight/volume ratio) was thickened with 0.5% dextrin. We made a barium jelly of normal consistency from the aforementioned barium water with 2% gelatin. The viscosity of thickened barium water corresponds approximately to that of nectar (150–300 mPa.s) and the viscosity of the jelly corresponds approximately to that of pudding (3900 mPa.s). In consideration of patient safety, we terminated the VF when aspiration

or penetration was expected to occur or at the time an actual event occurred. We used the worst PAS score to represent each patient's swallowing safety [15].

**Penetration-aspiration scale evaluation**

We evaluated each enrolled patient's swallowing by the PAS developed to provide reliable quantification of selected penetration and aspiration events observed during VF [31]. We used the PAS to evaluate and classify patients based on safety during swallowing.

Penetration is generally defined as passage into the larynx of material that does not pass below the vocal folds and corresponds to PAS 2 and 3. Aspiration is generally defined as passage of material below the level of the vocal folds and corresponds to PAS 6, 7, and 8. In this study, we divided patients into two groups according to the clinical risk and compared them. In the study of 95 normal subjects, of course, most were PAS 1, but a few PAS 2 and 3 were seen, while PAS 4 or more was never reported [32]. Moreover, laryngeal penetration without vocal fold contact is clinically found sometimes even in clearly healthy subjects [33]. Based on the above, we decided to group PAS 1, 2, 3 in

the same group. On the other hand, because dysphagia accompanying vocal fold contact could directly progress to aspiration, PAS 4 and 5 can be regarded as clinically higher risk situations compared to PAS 2 and 3. In order to compare patients in the two groups, we gathered the remaining PAS 4, 5, 6, 7, and 8 in the same group. In this way, we divided patients into two groups, PAS 1-3 and PAS 4-8. In this study, we described PAS 4-8 as high-risk dysphagia.

**Statistical analysis**

Statistical analyses were performed using PASW Statistics 18.0.0 (SPSS; Chicago, IL). We statistically compared categorical variables expressed as numbers using Fisher's exact test or the chi-square test as appropriate. We statistically compared continuous variables using an appropriate parametric (Student's *t*) test or nonparametric (Mann-Whitney *U*) test. We calculated odds ratio (OR) and 95% confidence interval (CI) using logistic regression analysis. We considered $P<0.05$ statistically significant.

## Results

The median age of enrolled 165 patients was 76.0, and the number of female patients was 53 (32.1%). The mean GNRI was 81.2, and 134 patients (81.2%) fulfilled the criteria of malnutrition. The 165 enrolled patients were classified into eight disease categories and two groups, PAS 1–3 and PAS 4–based on VF evaluation. No significant differences in the proportions of PAS 1–3 or PAS 4–8 among each category were revealed (Table 1).

Baseline characteristics as potential risk factors and GNRI<91.2 (Table 2). The number of patients with PAS 4–8 was 54 (32.7%). The median age of the patients with PAS 4-8 was not significantly higher than that of the patients with PAS 1–3 (77.0 versus 73.4, $P$=0.14). Neither BMI <18.5 nor serum albumin concentration <35 g/l was significantly associated with PAS 4–8. On the other hand, Fisher's exact probably test demonstrated that solely GNRI <91.2 was significantly associated with PAS 4–8 ($P$=0.034). The GNRI of patients with PAS 4–8 was significantly less than that of patients with PAS 1–3 (mean value, 77.7 ± 10.5 versus 83.0 ± 10.5, $P$=0.003).

For univariate analysis and forced entry multivariate analysis for detailed investigations (Table 3), we applied all potential risk factors except for albumin and BMI. We did not

use albumin and BMI only because GNRI includes both. A univariate analysis revealed that GNRI <91.2 was the only factor significantly associated with PAS 4–8. A multivariate logistic regression analysis with the forced entry method showed that only GNRI <91.2 was independently and significantly associated with PAS 4–8 (OR, 3.094; CI, 1.057-9.058; *P*=0.039).

## Discussion

This is the first report that clarifies a significant association between severe penetration and aspiration as evaluated by VF and precisely calculated malnutrition. A GNRI <91.2 triples the risk of serious swallowing dysfunction. However, careful consideration of the causal relationship between malnutrition and dysphagia is required. Malnutrition as a result of dysphagia is an easily comprehensible causality. Here we would rather discuss the possibility of the inverse causality, that is, dysphagia as a result of malnutrition.

### Effects of malnutrition on nerves and muscles involved in swallowing

Nutrient deprivation has previously been shown to cause alterations in muscle and nerve

function [34]. It is clear that malnutrition negatively affects muscle function. Especially as a consequence of protein-calorie malnutrition, there is a reduction in muscle weight, muscle fiber diameter, and impairment in the force of contraction and rate of relaxation of muscle fibers. The highly coordinated muscular events of swallowing depend on the activity of the central nervous system [35]. Protein-calorie malnutrition causes a significant reduction in motor nerve conduction velocity [36,37] and an increase in vacuolation, chromatolysis, and fibrolysis in both central and peripheral nerves microscopically [38]. Because neurotransmitter synthesis is susceptible to precursor control, a deficiency in tryptophan, tyrosine, and choline has been shown to decrease the synthesis of serotonin, norepinephrine, and acetylcholine, respectively [39]. Serotonin and norepinephrine participate in the swallowing reflex at the level of the nucleus solitarius [40].

**Relationship between malnutrition, neuromuscular dysfunction, and dysphagia**

Dysphagia obviously affects nutrition; meanwhile, malnutrition can exacerbate dysphagia through these neuromuscular dysfunctions [41]. The elderly easily fall into

this vicious circle. It seems to be difficult to break this reciprocal relationship, but it is not impossible. Swallowing rehabilitation is an effective approach to increasing safe oral intake, and recent research has demonstrated extended benefits related to improved nutritional status and reduced pneumonia rates [42]. Although there are pros and cons for tube feeding for patients with poor ingestion [43], we often encounter patients whose nutritional status have improved after gastrostomy and have again become capable of oral ingestion.

We hypothesize a triangular link between malnutrition, neuromuscular dysfunction, and dysphagia graphically (Figure 1). Being older is a background factor that can affect all three of these factors, so it is not included in this cycle. At present, we cannot confirm the physiological evidence of a causative relationship from malnutrition through neuromuscular dysfunction to dysphagia in the present study. In the future, it is necessary to measure actual muscle mass reduction and nerve dysfunction, which are caused by malnutrition, in relation to swallowing function.

**Dysphagia and malnutrition in the elderly**

In this study, simply being elderly was not associated with dysphagia. Having malnutrition had a stronger effect on swallowing function than being elderly. Subtle changes that occur with age in swallowing function may be compensatory protective mechanisms rather than the result of decreased muscle mobility or reaction times, and not indicative of impairment [41]. Everyone is getting older equally and there is no way to resist it. It seems to be important to accurately grasp the factors other than aging that affect swallowing and to take measures against them individually. Malnutrition is one of the important causes of dysphagia in the elderly.

The causes of malnutrition of elderly people are diverse [44]. Of course, various pathological conditions cause malnutrition, but many, even healthy, elderly people fail to adequately consume food and experience loss of weight. Aging-associated changes in the regulation of appetite and the lack of hunger have been termed 'the anorexia of aging.' The etiology of the anorexia of aging is multifactorial and includes a combination of physiological changes and social factors associated with aging, such as a decline in the senses of smell and taste, reduced central and peripheral drives to eat, delayed gastric emptying, oral health status, low income and poverty, and loneliness and

social isolation [45]. In order to overcome the problem of malnutrition, a team approach including medical doctors, dentists, nurses, public health nurses, nutritionists, and therapists is important in both the acute phase and in the pre-disease community dweller stages.

**Clinical usefulness of GNRI**

Originally the nutritional risk index (NRI) was developed by Buzby et al. [22] to evaluate the severity of postoperative complications using the serum albumin concentration and body weight, and 100 was set as a normal threshold. Faced with the difficulty in identifying the usual body weight of elderly or hospitalized patients in the real world, Bouillanne et al. [23] proposed GNRI using the ideal body weight calculated from the Lorentz formula instead of the usual body weight in NRI. Finally, Yamada et al. [24] succeeded in simplifying the calculation of GNRI by using BMI of 22.0 $kg/m^2$ instead of the Lorentz formula, without lowering its accuracy. In this way, GNRI has evolved and became a universal evaluation method that can now be easily used by anyone. In this study, we adopted BMI 22 and GNRI<91.2 like a previous study of

elderly Japanese [24]. However, in many study results, BMI 22 is not always the only optimal value under all circumstances. The ideal BMI might be different depending on age, sex, race, and so on. Even in Japan, which has an unprecedented super-aged society, many aspects of the nutrition and appropriate weight of the elderly are unknown; therefore, future research is required [46]. In using GNRI with BMI, we need to pay attention to the above points at the present time.

GNRI needs only three variables that are easy to obtain from patients, actual body weight, body height, and serum albumin concentration, and the combination is precise. The serum albumin concentration remains an unreliable indicator of nutritional status because it may be more related to inflammation or hydration status than to malnutrition [47]. Dehydration raises the concentration of serum albumin. Meanwhile, overhydration decreases the concentration of serum albumin. In short, fluctuations of extracellular fluid volume move the albumin concentration and body weight in opposite directions [48]. The greatest advantage of GNRI is that it can counteract the contradictory changes in albumin concentration and body weight. Moreover, in the GNRI formula, the weight ratio is set as equal to 1 if the actual body weight was higher than the ideal body weight.

This prevents underdiagnosing malnourished patients who are overweight. On the other hand, GNRI detects malnourished patients effectively by combining the effects of low albumin concentration and low BMI. That is why GNRI alone showed a significant difference between PAS 1-3 and PAS 4-8 in the present study.

**Malnutrition and dysphagia of acute disease patients**

In recent years, it has been known that the prevalence of malnutrition is very high among older patients with oropharyngeal dysphagia associated with not only chronic but also acute conditions [49]. In fact, nutrition status is often neglected by medical staff during an acute illness [50]. In our study, 81.2% of acute patients suspected of dysphagia were clearly malnourished. Nutritional disorders are comorbid diseases that are often associated with stroke [51,52], cancer [53], chronic heart failure [54], and COPD [55, 56]. When we encounter patients who might have swallowing dysfunction, we should assess the nutritional status first during acute management. The easily calculated GNRI <91.2 from serum albumin concentration and body height and weight may predict high-risk dysphagia precisely before evaluation with VF.

In this study, PAS, which has been widely used for more than 20 years, was used to evaluate findings of airway invasion obtained as a result of VF. There is no doubt about the usefulness of PAS, which is an objective numerical evaluation scale, and PAS will continue to be used to scientifically utilize the results of VF. In general, because the likelihood of developing pneumonia is directly related to the severity of PAS [57], a higher PAS value is more likely to be considered severe; thus, in this study we divided patients into two groups and described PAS 4-8 as high-risk dysphagia. However, in recent years, there have been other studies that suggest the relationship is not straightforward [58], and a categorical revision of PAS was proposed very recently [15]. If this revision is widely accepted, the relationship between swallowing and nutrition can be examined more accurately.

Whether improvement of nutritional status affects swallowing function in the acute phase is still unknown. Nii et al. suggested that nutritional improvement and energy intake at admission are associated with recovery of activities of daily living after cerebrovascular diseases [59]. In cancer, early identification of patients who are malnourished or at risk of malnutrition is known to promote recovery and improve

prognosis [60]. Moreover, early nutritional intervention is cost effective because it reduces complication rates and length of hospital stay [60]. Our future task is to clarify the mechanism of a positive linkage demonstrating that improving nutritional status during the acute phase improves swallowing and thereby improves a patient's prognosis.

**Limitations**

This study had several limitations. First, the results of this research have limited effectiveness due to the small number of cases. To determine the association between dysphagia and nutrition status with sufficient statistical power, more patients should be studied. Second, because this was a retrospective single-center study, we should not extrapolate the results generally. We are organizing a prospective study to reveal the causative association between dysphagia and malnutrition with more cases.

## Conclusions

This is the first study to show in which malnutrition defined as GNRI <91.2 is

associated with high-risk dysphagia as correctly evaluated by VF in acute patients. Malnutrition defined as GNRI <91.2 is independently associated with high-risk dysphagia among representative acute risk factors. Further, GNRI <91.2 is a more reliable prognostic indicator of dysphagia in acute patients than traditional indices that use albumin or BMI alone. We propose the importance and necessity of evaluating nutritional status to predict the dysphagia risk of patients in the acute phase.

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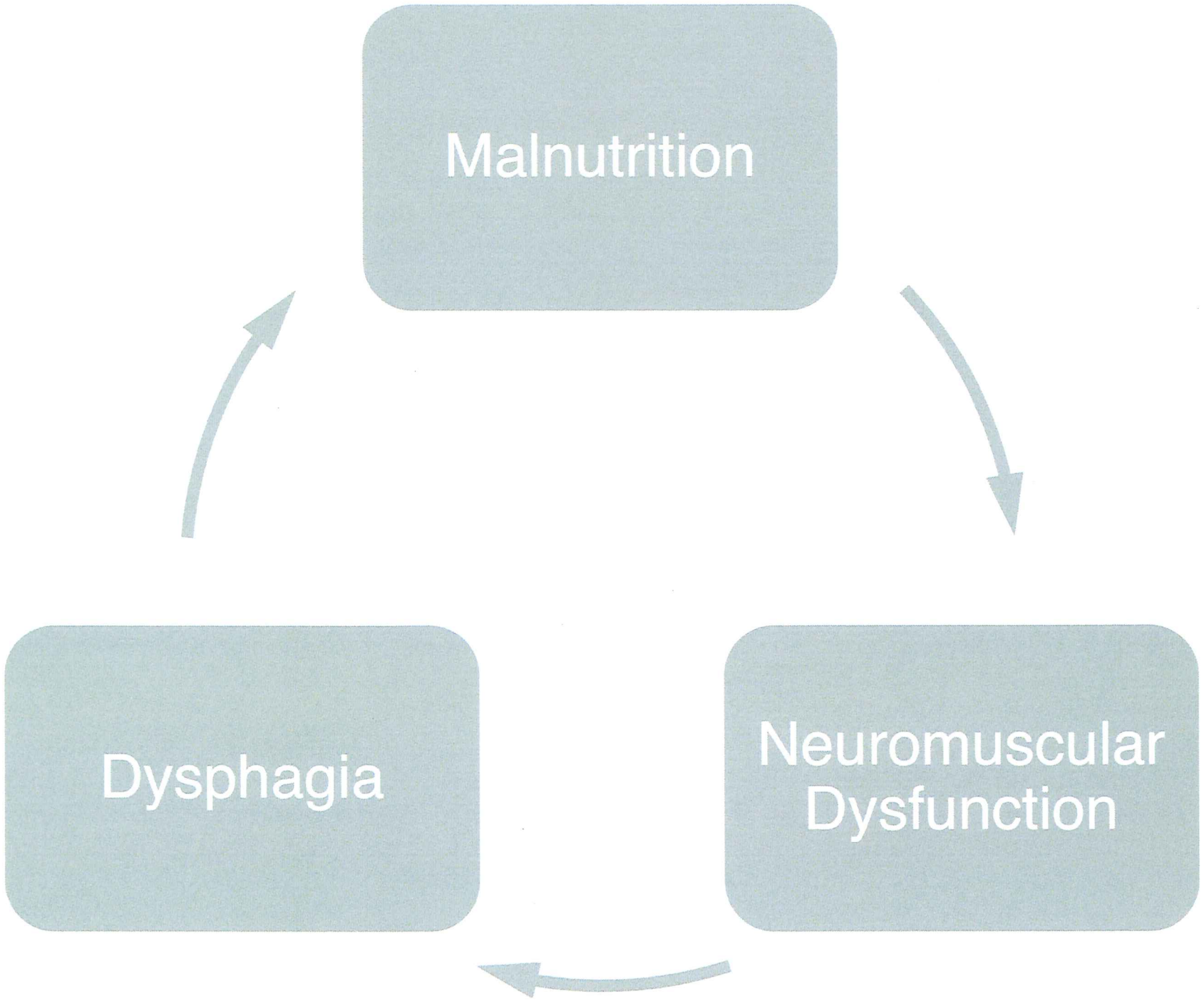
Malnutrition
Neuromuscular Dysfunction
Dysphagia

Table1. Categories of diesases and the number of patients of each PAS. Chi-square for indepence test did not reveal any significant association between disease classification and PAS1-3 or PAS4-8.

| | PAS1 | PAS2 | PAS3 | PAS1-3 | PAS4 | PAS5 | PAS6 | PAS7 | PAS8 | PAS4-8 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| brain tumors | 6 | 1 | 0 | 7 (6.3%) | 0 | 1 | 0 | 0 | 0 | 1 (1.9%) | 8 |
| cardiovascular diseases | 15 | 3 | 0 | 18 (16.2%) | 1 | 0 | 0 | 2 | 4 | 7 (13.0%) | 25 |
| malignancies | 9 | 2 | 0 | 11 (9.9%) | 1 | 3 | 0 | 3 | 3 | 10 (18.5%) | 21 |
| musculoskeletal disorders | 7 | 1 | 0 | 8 (7.2%) | 0 | 1 | 1 | 0 | 0 | 2 (3.7%) | 10 |
| neurological disorders | 13 | 4 | 2 | 19 (17.1%) | 1 | 4 | 0 | 2 | 3 | 10 (18.5%) | 29 |
| pneumonia | 10 | 3 | 0 | 13 (11.7%) | 1 | 2 | 0 | 2 | 0 | 5 (9.3%) | 18 |
| stroke | 12 | 7 | 1 | 20 (18.0%) | 0 | 2 | 1 | 3 | 8 | 14 (25.9%) | 34 |
| other diseases | 9 | 4 | 2 | 15 (13.5%) | 1 | 1 | 0 | 2 | 1 | 5 (9.3%) | 20 |
| | 81 | 25 | 5 | 111 (100%) | 5 | 14 | 2 | 14 | 19 | 54 (100%) | 165 |

Abbreviation: PAS, penetration-aspiration scale.

Table2. Profiles of patients assorted by PAS1-3 or 4-8

| | PAS1-3<br>n=111 | PAS4-8<br>n=54 | P |
|---|---|---|---|
| Median age | 73.4 | 77.0 | 0.144 |
| Female sex | 38 (34.2%) | 15 (27.8%) | 0.479 |
| Congestive heart disease | 24 (21.6%) | 13 (24.1%) | 0.843 |
| Hypertension | 71 (64.0%) | 31 (57.4%) | 0.495 |
| Age>75 y | 62 (55.9%) | 33 (61.1%) | 0.615 |
| Diabetes mellitus | 37 (33.3%) | 20 (37.0%) | 0.728 |
| PH of Stoke/TIA | 18 (16.2%) | 12 (22.2%) | 0.392 |
| Vascular disease | 26 (23.4%) | 9 (16.7%) | 0.418 |
| Chronic kidney disease | 35 (31.5%) | 16 (29.6%) | 0.859 |
| COPD | 21 (18.9%) | 9 (16.7%) | 0.831 |
| Alb<35g/dl | 83 (74.8%) | 47 (87.0%) | 0.103 |
| BMI<18.5 | 28 (25.2%) | 20 (37.0%) | 0.144 |
| GNRI<91.2 | 85 (76.6%) | 49 (90.7%) | 0.034 |
| Mean GNRI | 83.0±10.5 | 77.7±10.5 | 0.003 |

Abbreviations: Alb, serum albumin concentration; BMI, body mass index; COPD, chronic obstructive pulmonary disease; GNRI, geriatric nutritional risk index; PAS. penetration-aspiration scale; PH, previous history; TIA, transient ischemic attack.

Table3. Statistical analysis of 165 patients and the variates appertaining to the PAS 4-8

| | univariate analysis OR (95% CI) | P | multivariate analysis OR (95% CI) | P |
|---|---|---|---|---|
| Female sex | 0.739 (0.362-1.507) | 0.405 | 0.627 (0.291-1.352) | 0.627 |
| Congestive heart disease | 1.149 (0.532-2.483) | 0.723 | 1.144 (0.480-2.726) | 0.762 |
| Hypertension | 0.759 (0.391-1.475) | 0.417 | 0.817 (0.402-1.660) | 0.577 |
| Age>75 y | 1.242 (0.640-2.410) | 0.522 | 1.095 (0.525-2.283) | 0.809 |
| Diabetes mellitus | 1.176 (0.597-2.319) | 0.639 | 1.039 (0.494-2.184) | 0.921 |
| PH of Stoke/TIA | 1.476 (0.653-3.339) | 0.35 | 1.498 (0.623-3.603) | 0.367 |
| Vascular disease | 0.654 (0.282-1.514) | 0.321 | 0.571 (0.221-1.474) | 0.247 |
| Chronic kidney disease | 0.914 (0.450-1.856) | 0.804 | 0.941 (0.428-2.067) | 0.88 |
| COPD | 0.857 (0.363-2.023) | 0.725 | 0.779 (0.300-2.020) | 0.607 |
| GNRI<91.2 | 2.998 (1.081-8.310) | 0.035 | 3.094 (1.057-9.058) | 0.039 |

Abbreviations: Alb, serum albumin concentration; BMI, body mass index; CI, confidence intervals; COPD, chronic obstructive pulmonary disease; GNRI, geriatric nutritional risk index; OR, odds ratio; PAS. penetration-aspiration scale; PH, previous history; TIA, transient ischemic attack.