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Research Article

A Predictive Model and Survival Analysis for Tube Feeding in ALS Patients: A Prospective Cohort Study in a Chinese ALS Clinic

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Objectives. Tube feeding is an effective way to provide nutritional support for amyotrophic lateral sclerosis (ALS) patients with severe dysphagia. Currently, the predictors of tube feeding and the survival affected by tube feeding were poorly studied in Chinese ALS patients. Therefore, we aimed to explore predictive factors and establish a prediction model to quantitatively predict the risk of tube feeding. Furthermore, we explored the survival benefit provided by tube feeding. *Methods*. In this longitudinal, prospective cohort study, we included patients diagnosed with ALS using the Awaji criteria at the ALS clinic in Huashan Hospital. Follow-up was conducted by telephone interview from January 1, 2019, to December 30, 2021, or until death. All statistical analyses were performed using R software. *Results*. Overall, 218 patients were recruited for the study. The multivariate Cox regression analysis showed a high ALSFRS-R slope (adjusted hazard ratio (aHR) = 4.94 (95% confidence interval (95% CI: 2.26-10.81), $p < 0.001$), low bulbar score (aHR = 0.81 (95% CI: 0.69-0.96), $p = 0.01$), history of ischemic stroke (aHR = 5.69 (95% CI: 1.3-24.82), $p = 0.02$), and bulbar involvement (aHR = 11.87 (95% CI: 1.42-99.31), $p = 0.02$) as independent risk factors of tube feeding. The nomogram model was established with moderate discrimination and calibration. Among 71 ALS patients with tube feeding indication, 33.8% accepted gastrostomy suggestion and 14.1% had nasogastric tube (NGT) insertion. However, gastrostomy and NGT did not accelerate disease progression (aHR = 0.57 (95% CI: 0.20-1.67), $p = 0.31$ and aHR = 1.72 (95% CI: 0.43-6.88), $p = 0.43$, respectively). *Conclusions*. We developed a nomogram that could be a prediction tool to predict individual timing of tube feeding for ALS patients. In addition, we found that gastrostomy and NGT did not affect ALS patients' survival.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder causing progressive muscle atrophy, dysarthria, dysphagia, and respiratory failure [1]. The standardized ALS prevalence and incidence were 2.97 per 100,000 people and 1.62 per 100,000 person-years in mainland China, respectively [2]. The median survival time for Chinese ALS patients was 71 months [3]. It is also significantly affected by dysphagia, a common symptom in ALS patients, resulting in aspiration, malnutrition, and mortality [4]. When dysphagia becomes severe, tube feeding may be an effective way to provide nutritional support for ALS patients [5].

Tube feeding is considered reasonable; however, nasogastric tube (NGT) as one of the methods of tube feeding was reported to be associated with high risk of pneumonia and asphyxia for the long-term use [6]. Gastrostomy is more recommended by the guidelines, which could improve patients' nutritional status and stabilize their body weight effectively [5, 7, 8]. Still, there is little convincing evidence that supports the survival benefit or definite life quality improvement of gastrostomy in ALS patients [9], which needs to be further studied. Furthermore, there is insufficient evidence to determine the timing of the gastrostomy procedure in ALS patients. Individualized timing should be recommended according to each patient's bulbar symptom,

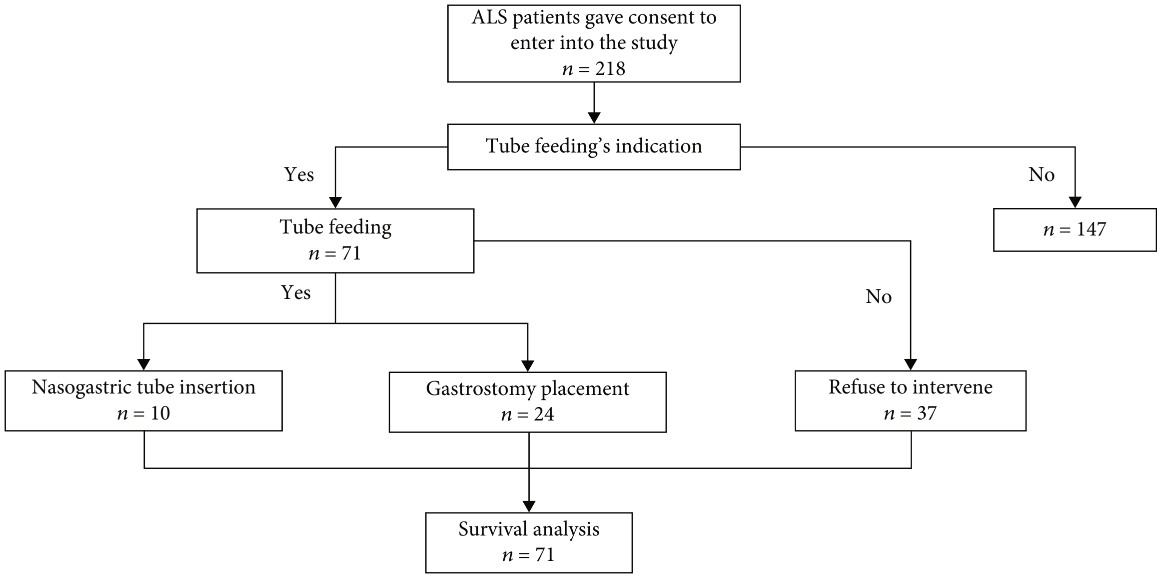

Figure 1: Study profile. Among 218 of ALS patients, 71 of ALS patients met the criteria of tube feeding, 24 of patients eventually received gastrostomy, 10 of patients had nasogastric tube insertion, and 37 of patients refuted to have swallow intervention.

nutritional status, respiratory status, and general condition [5]. Guidelines recommend early gastrostomy in ALS patients because a delayed procedure might cause an increased risk of respiratory complications, dehydration, surgery complications, and mortality [5, 8, 10].

Thus, the timing and acceptance of gastrostomy in ALS patients are still unknown. Currently, there were only few studies of gastrostomy in Chinese ALS patients, and the data about risk factors of gastrostomy were lacking in Chinese patients. Therefore, we established a prospective single-center cohort of ALS patients in eastern China to explore the predictive factors associated with tube feeding in these hospital-based ALS patients. In this study, a predictive model was also established to quantitatively predict the risk of receiving tube feeding for individual patients. According to their tube feeding acceptance, survival analysis was also conducted in ALS patients with tube feeding treatment.

2. Methods

2.1. Study Design and Participants. We conducted a prospective longitudinal cohort study at the ALS clinic in Huashan Hospital, China, from January 1st, 2019, to December 30th, 2021. We enrolled 218 patients diagnosed with ALS according to the Awaji criteria [11].

2.2. Ethics. The study was approved by the Huashan Institutional Review Board under the following code: KY2019-275, 01 on 15th January 2019. All patients who agreed to participate in the study provided written informed consent before data collection.

2.3. Data Collection. For each patient, we collected data at their first visit to our ALS clinic consisting of the fundamental clinical characteristics regarding age at disease onset, sex, site of onset, diagnostic delay (time from onset to diagnosis), body mass index (BMI) at baseline, weight loss (in kilogram) after disease onset, a revised ALS functional rating scale that incorporates assessments of respiratory function (ALSFRS-R) [12], and past history. The patient's respiratory condition and ALSFRS-R score were prospectively collected during the follow-up. Whether there was noninvasive ventilator (NIV) support, gastrostomy, or NGT intervention was also asked during the disease course. Survival status was followed up from January 1, 2019, to December 30, 2021, or until death, using telephone interviews.

2.4. Intervention. We found that ALS patients with weight loss of over 10% or mealtime of over 45 minutes were unwilling to receive gastrostomy in our clinic, so the indication of gastrostomy in our patients was the swallow function of the bulbar score (item 3 in ALSFRS-R score) that was lower than 3.

2.5. Outcome Measurements. An ALSFRS-R score was used by two professional neurologists to evaluate ALS patients' motor function, consisting of the bulbar score, fine motor score, respiratory score, and gross motor score [12, 13]. The number of body regions involved (NBRI) and the involvement of different segments (bulbar, upper limbs, lower limbs, and respiratory function) were extracted from the ALSFRS-R score [14]. The slope of ALSFRS-R progression is calculated as follows: (48 − ALSFRS-R at diagnosis)/(duration from onset to diagnosis) [15].

2.6. Statistical Analysis. All statistical comparisons and data visualizations were performed using R (V. 4.1.2). Quantitative data with normal distribution were presented as means ± standard deviation (SD), and data without normal distribution were described as median and quartile. Qualitative data were presented as frequency/ratio. To compare baseline characteristics, we used Student's t-test, Wilcoxon signed-

Table 1: The clinical characteristics of ALS patients stratified by the tube feeding at diagnosis or during follow-up.

Variables	Tube feeding No ($n = 184$) n (%) or mean (SD) or median (IQR)	Tube feeding Yes ($n = 34$) n (%) or mean (SD) or median (IQR)	Total ($n = 218$) n (%) or mean (SD) or median (IQR)	Statistics	p value
At baseline					
Sex				χ^2	0.592
Male	115 (62.5)	19 (55.9)	134 (61.5)		
Female	69 (37.5%)	15 (44.1%)	84 (38.5%)		
Familiar ALS	22 (12.0)	3 (8.8)	25 (11.5)	Fisher's exact test	0.774
Age of onset (y)	53.21 (12.42)	58.09 (12.37)	53.97 (12.51)	t-test	**0.036**
Death	40 (21.7)	14 (41.2)	54 (24.8)	χ^2	**0.028**
Site of disease onset				χ^2	**<0.001**
Bulbar	24 (13.0)	16 (47.1)	40 (18.3)		
Spinal	160 (87.0%)	18 (52.9%)	178 (81.7%)		
Time to diagnose (m)	10.50 (6.00, 18.00)	9.00 (6.25, 12.00)	10.00 (6.00, 16.00)	Mann–Whitney test	0.257
Weight loss (%)	81 (44.0)	22 (64.7)	103 (47.2)	χ^2	**0.042**
Weight loss (kg)	0.00 (0.00, 5.00)	5.00 (0.00, 10.00)	0.00 (0.00, 5.00)	Mann–Whitney test	**0.001**
BMI at baseline (kg/m^2)	23.00 (21.00, 25.00)	22.00 (18.00, 24.00)	23.00 (20.00, 25.00)	Mann–Whitney test	**0.029**
NBRI				Fisher's exact test	**<0.001**
1	58 (31.5)	2 (5.9)	60 (27.5)		
2	57 (31.0)	5 (14.7)	62 (28.4)		
3	40 (21.7)	9 (26.5)	49 (22.5)		
4	22 (12.0)	18 (52.9)	40 (18.3)		
Bulbar involvement	78 (42.4)	32 (94.1)	110 (50.5)	Fisher's exact test	**<0.001**
Upper limb involvement	124 (67.4)	28 (2.4)	152 (69.7)	Fisher's exact test	0.104
Lower limb involvement	129 (70.1)	30 (88.2)	159 (72.9)	Fisher's exact test	**0.035**
Respiratory involvement	49 (26.6)	21 (61.8)	70 (32.1)	χ^2	**<0.001**
ALSFRS-R score	40.00 (36.00, 44.00)	31.00 (18.00, 36.75)	39.00 (35.00, 43.00)	Mann–Whitney test	**<0.001**
Bulbar score	12.00 (10.00, 12.00)	5.50 (2.00, 10.00)	11.00 (9.00, 12.00)	Mann–Whitney test	**<0.001**
Fine motor score	9.00 (7.00, 11.00)	5.00 (2.00, 8.75)	9.00 (6.00, 11.00)	Mann–Whitney test	**<0.001**
Gross motor score	9.00 (7.00, 11.00)	7.00 (3.00, 9.00)	9.00 (6.00, 11.00)	Mann–Whitney test	**0.004**
Respiratory score	12.00 (11.00, 12.00)	11.00 (9.00, 12.00)	12.00 (11.00, 12.00)	Mann–Whitney test	**<0.001**
ALSFRS-R slope	0.42 (0.22, 0.91)	0.84 (0.56, 1.37)	0.48 (0.25, 0.98)	Mann–Whitney test	**<0.001**
Ischemic stroke	1 (0.5)	3 (8.8)	4 (1.8)	Fisher's exact test	**0.013**

Table 1: Continued.

Variables	Tube feeding No ($n = 184$) n (%) or mean (SD) or median (IQR)	Tube feeding Yes ($n = 34$) n (%) or mean (SD) or median (IQR)	Total ($n = 218$) n (%) or mean (SD) or median (IQR)	Statistics	p value
During follow-up					
NIV routine users	37 (20.1)	20 (58.8)	57 (26.1)	χ^2	**<0.001**
Dyspnea	75 (40.8)	26 (76.5)	101 (46.3)	χ^2	**<0.001**
Dysphagia	80 (43.5)	24 (70.6)	104 (47.7)	χ^2	**0.007**
Past history					
Hyperlipidemia[a]	21 (11.4)	4 (11.8)	25 (11.5)	Fisher's exact test	1
Hypertension[a]	56 (30.4)	11 (32.4)	67 (30.7)	Fisher's exact test	0.841
Diabetes[a]	13 (7.1)	1 (2.9)	14 (6.4)	Fisher's exact test	0.702
Drinking[a]	55 (29.9)	12 (35.3)	67 (30.7)	χ^2	0.671
Smoking[a]	72 (39.1)	13 (38.2)	85 (39.0)	χ^2	1
Depression[a]	4 (2.2)	0 (0.0)	4 (1.8)	Fisher's exact test	1
Anxiety[a]	3 (1.6)	1 (2.9)	4 (1.8)	Fisher's exact test	0.495
Malignancy[a]	6 (3.3)	1 (2.9)	7 (3.2)	Fisher's exact test	1
Allergy[a]	15 (8.2)	2 (5.9)	17 (7.8)	Fisher's exact test	1
Exposure of toxic substances[a]	31 (16.8)	6 (17.6)	37 (17.0)	χ^2	1
Trauma[a]	57 (31.0)	9 (26.5)	66 (30.3)	χ^2	0.747
Surgical history[a]	69 (37.5)	12 (36.4)	81 (37.3)	χ^2	1

Patients with bulbar onset, older onset age, early body weight loss, low BMI at baseline, history of ischemic stroke, and high ALSFRS-R slope tended to have tube feeding. In addition, the patient with a low ALSFRS-R score and subregion score or NBRI > 2 at baseline was more likely to have tube feeding. The percentage of ALS patients with bulbar, lower limb, or respiratory involved at baseline was higher in the tube feeding group. During the follow-up, NIV users and patients with dyspnea or dysphagia were more likely to have tube feeding. The mortality rate of patients with tube feeding was higher than those without tube feeding. ALS patients with past history at diagnosis (such as hyperlipidemia, hypertension, diabetes, drinking, smoking, depression, anxiety, malignancy, allergy, exposure of toxic substances, trauma, and surgical history) had no difference in tube feeding. Familiar ALS patients did not have the higher tube feeding rate. Note: ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale revised; BMI: body mass index; a: at baseline; y: year; m: month; kg: kilogram; NIV: noninvasive ventilation; NBRI: body regions involved; *n*: number; *p*: probability. In bold: p value < 0.05.

rank test, or Fisher's exact test determined by the type and distribution of each variable without modification for multiple comparisons.

The univariate Cox regression analysis was performed to identify predictors for early tube feeding procedures. All p values were two-sided, and predictive factors with a p value lower than 0.1 in univariate analysis were included in a multivariate analysis. Independent predictors were identified in the multivariate analysis and, finally, used to create the nomogram.

2.7. Prediction Model Building and Validation. The model performance was assessed by discrimination and calibration [16]. The area under the receiver operating characteristic (ROC) curve and concordance index (C-index) determined the discrimination, which ranged from 0.5 (no discrimination) to 1 (perfect discrimination) [17]. The calibration of the model was presented by a visual calibration plot comparing the predicted and actual tube feeding-free probability. In addition, the nomogram was subjected to 1,000 bootstrap resamples for internal validation [18].

2.8. Survival Analysis. To determine the effect of gastrostomy on survival, we included variables with a p value lower than 0.1 in the univariate analysis into the multivariate Cox regression model. Survival time was analyzed from the date of disease onset until the death of the ALS patient or the censoring date. The proportional hazard (PH) assumptions were tested using an interaction-with-time method. p values less than 0.05 were considered to be statistically significant.

Table 2: Factors associated with tube feeding in univariate and multivariate analysis with the Cox regression analysis ($N = 218$).

Variables	Univariate analysis cHR (95% CI)	Univariate analysis p value	Multivariate analysis aHR (95% CI)	Multivariate analysis p value
Sex	0.72 (0.37-1.42)	0.34		
Age of onset (y)	1.03 (1.00-1.06)	**0.04**	1.04 (1.00-1.08)	0.05
Bulbar onset	4.99 (2.49-9.99)	**<0.001**	0.68 (0.22-2.06)	0.49
Time to diagnose (m)	0.93 (0.89-0.98)	**0.002**	0.95 (0.90-1.01)	0.12
ALSFRS-R score[a]	0.92 (0.90-0.94)	**<0.001**		
ALSFRS-R slope[a]	6.36 (3.89-10.41)	**<0.001**	4.94 (2.26-10.81)	**<0.001**
NBRI[a]	2.65 (1.82-3.84)	**<0.001**	0.58 (0.12-2.79)	0.49
Bulbar involvement[a]	19.41 (4.64-81.28)	**<0.001**	11.87 (1.42-99.31)	**0.02**
Upper limb involvement[a]	1.56 (0.64-3.80)	0.32		
Lower limb involvement[a]	3.22 (1.13-9.15)	**0.03**	1.89 (0.12-30.03)	0.65
Respiratory involvement[a]	4.53 (2.26-9.06)	**<0.001**	1.98 (0.31-12.53)	0.47
BMI [a]	0.86 (0.78-0.95)	**0.003**	1.09 (0.95-1.26)	0.23
Weight loss (kg)[a]	1.1 (1.05-1.14)	**<0.001**	1.05 (0.95-1.15)	0.34
Weight loss (%)[a]	2.55 (1.26-5.16)	**0.01**	0.85 (0.26-2.83)	0.79
Bulbar score[a]	0.74 (0.69-0.80)	**<0.001**	0.81 (0.69-0.96)	**0.01**
Fine motor score[a]	0.85 (0.78-0.93)	**<0.001**	1.05 (0.87-1.28)	0.59
Gross motor score[a]	0.86 (0.79-0.95)	**0.002**	0.98 (0.81-1.20)	0.87
Respiratory score[a]	0.81 (0.74-0.89)	**<0.001**	1.12 (0.89-1.40)	0.33
NIV routine users[b]	4.91 (2.47-9.75)	**<0.001**	1.86 (0.59-5.87)	0.29
History of ischemic stroke[a]	8.76 (2.65-28.97)	**<0.001**	5.69 (1.3-24.82)	**0.02**
Dyspnea[b]	4.39 (1.98-9.75)	**<0.001**	1.00 (0.29-3.42)	0.99

Factors associated with tube feeding with p value lower than 0.1 using the univariate Cox regression were enrolled in the multivariate Cox regression analysis. High ALSFRS-R slope, low bulbar score, history of ischemic stroke, and bulbar involvement were identified as independent risk factors of tube feeding using the multivariate Cox regression. Note: ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale revised; NBRI: body regions involved; BMI: body mass index; NIV: noninvasive ventilation; aHR: adjusted hazard ratio; cHR: crude hazard ratio; y: year; m: month; kg: kilogram; 95% CI: 95% confidence interval; a: at baseline; b: during follow-up; n: number. In bold: p value < 0.05.

3. Results

3.1. Clinical Characteristics. Between January 1, 2019, and December 30, 2021, 218 patients were enrolled in the study (Figure 1). The clinical characteristics of these ALS patients are shown in Table 1. The mean age of onset was 53.97 years (SD 12.51) and 134 (61.5%) were male. The differences between the tube feeding and the nontube feeding groups are summarized in Table 1. Patients with bulbar onset ($p < 0.001$), older onset age ($p = 0.036$), early body weight loss ($p = 0.042$), low BMI at baseline ($p = 0.029$), history of ischemic stroke ($p = 0.013$), and high ALSFRS-R slope ($p < 0.001$) were more likely to accept tube feeding suggestion. In addition, patients with a low ALSFRS-R score, a low subregion score, or NBRI > 2 (all $p < 0.01$) at baseline were more likely to accept tube feeding. Those ALS patients with bulbar ($p < 0.001$), lower limb ($p = 0.035$), or respiratory involvement at baseline ($p < 0.001$) had a higher rate of tube feeding. During the follow-up, NIV users (58.8%) and patients with symptoms such as dyspnea or dysphagia (all $p < 0.01$) were more likely to have tube feeding. The mortality rate of patients with tube feeding (41.2%) was significantly higher, compared to those without tube feeding ($p = 0.028$).

3.2. Prediction Model and Validation. We performed the multivariate Cox regression analysis enrolling the factors with p value lower than 0.1 in the univariate Cox regression analysis. We identified a high ALSFRS-R slope (adjusted hazard ratio (aHR) = 4.94 (95% confidence interval (95% CI): 2.26-10.81), $p < 0.001$), low bulbar score (aHR = 0.81 (95% CI: 0.69-0.96), $p = 0.01$), history of ischemic stroke (aHR = 5.69 (95% CI: 1.30-24.82), $p = 0.02$), and bulbar involvement (aHR = 11.87 (95% CI: 1.42-99.31), $p = 0.02$) as independent risk factors of tube feeding (Table 2). All independent risk factors met the PH assumption. We created the nomogram to predict the timing of the tube feeding procedure using ALSFRS-R slope, bulbar subscore, history of ischemic stroke, and bulbar involvement at baseline (Figure 2). The C-index of this predictive model was 0.89 (95% CI: 0.84-0.93), and the area under curve (AUC) was 0.84 with the ROC curve (Figure 3(a)), indicating the favorable discrimination of patients receiving tube feeding by this predictive model. Furthermore, the calibration curves of 1-year, 2-year, and 3-year tube feeding-free probability matched the ideal reference line pretty well using internal validation via 1,000 bootstraps (Figures 3(b)–3(d)). These results both revealed the excellent predictive efficiency of our predictive model.

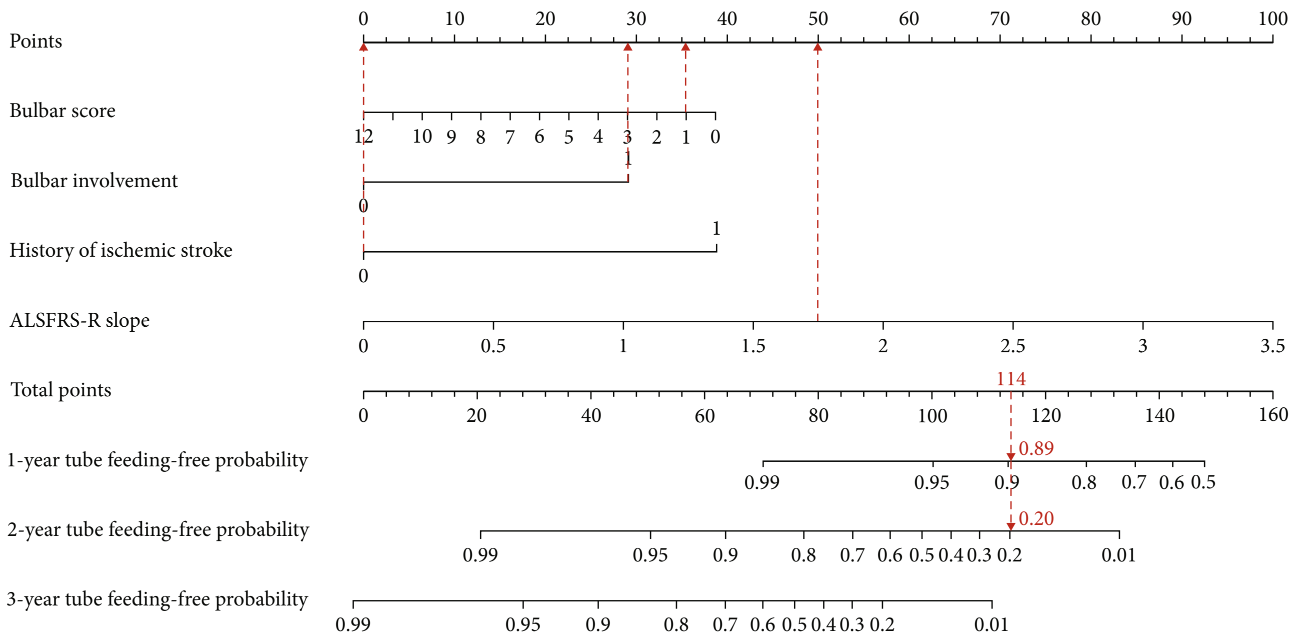

Figure 2: A nomogram for tube feeding prediction of ALS patients. To use the nomogram, mark patient values at each axis, draw a straight line perpendicular to the point axis, and sum the points for all variables. Next, mark the sum on the total point axis and draw a straight line perpendicular to the probability axis. For example, the patient had 1 of bulbar score, a bulbar involvement at baseline, 1.76 of ALSFRS-R slope, and without a history of ischemic stroke. To use the nomogram, red lines and arrows are drawn upward to determine the points received by bulbar score, bulbar involvement at baseline, ALSFRS-R slope, and history of ischemic stroke; the sum (about 114) of these points is located on the total point axis, and a line is drawn downward to the probability axes to determine the tube feeding-free probability of 1 year (about 89%) and 2 years (about 20%).

3.3. Survival Analysis. Among the 71 (32.6%) ALS patients who met the criteria of tube feeding, 24 (33.8%) patients eventually received gastrostomy, 10 (14.1%) patients had NGT insertion, and 37 (52.1%) refused to have swallow intervention. The differences between the tube feeding (gastrostomy or NGT) and the nonswallow intervention groups are summarized in Table 3. The clinical characteristics of these ALS patients, stratified by death, are shown in Table 4. The median survival time from disease onset was 34.00 months (IQR: 23.25, 43.25) in the gastrostomy group, 35.00 months (IQR: 28.75, 42.25) in the NGT group, and 37.00 months (IQR: 23.00, 48.00) in the nonswallowing intervention (NWI) group ($p = 0.49$). The Kaplan-Meier survival curves for gastrostomy, NGT, and NWI groups are shown in Figure 4.

We did the multivariate Cox regression analysis enrolling the factors with p value lower than 0.1 in the univariate Cox regression analysis. We identified male gender (aHR = 3.74 (95% CI: 1.34-10.44), $p = 0.01$), high ALSFRS-R slope (aHR = 9.20 (95% CI: 3.74-22.64), $p < 0.001$), high fine motor score (aHR = 1.25 (95% CI: 1.06-1.48), $p = 0.01$), history of ischemic stroke (aHR = 6.34 (95% CI: 1.27-31.63), $p = 0.03$), and bulbar onset (aHR = 4.89 (95% CI: 1.07-22.36), $p = 0.04$) as independent risk factors of death (Table 5). The multivariate Cox regression analysis showed that gastrostomy did not accelerate disease progression and might help on survival time (aHR = 0.57 (95% CI: 0.20-1.67), $p = 0.31$) compared with the NWI group, while NGT insertion had a negative trend in ALS patients (aHR = 1.72 (95% CI: 0.43-6.88), $p = 0.43$), though both without significant difference. In addition, gastrostomy had a trend of better survival in ALS patients than NGT insertion (aHR = 0.61 (95% CI: 0.13-2.78), $p = 0.52$), though without statistical significance.

4. Discussion

In this clinic-based single-center prospective cohort study, we summarized the characteristic, including rapid disease progression, low bulbar subscore, bulbar involvement at baseline, and history of ischemic stroke, and built a predictive model of tube feeding in ALS patients by a nomogram. Then, we assessed the survival rate of ALS patients who were indicated for tube feeding and finally received gastrostomy, NGT insertion, or no intervention during the follow-up, and we found that gastrostomy might positively affect the ALS patients' survival, but NGT insertion might have an opposite effect, though without significant difference, which were consistent with some observational studies [19–21]. Importantly, we evaluated the effect of gastrostomy on ALS patients who are indicated for tube feeding with a swallowing score of 2 or less, which was different from most previous studies.

Recently, only a few studies were conducted to evaluate the risk factors for tube feeding in Chinese ALS patients. In our present study, high ALSFRS-R slope and low bulbar function score were demonstrated to be associated with tube feeding, which was similar to a French study. This French cohort found that the faster neurological decline and bulbar

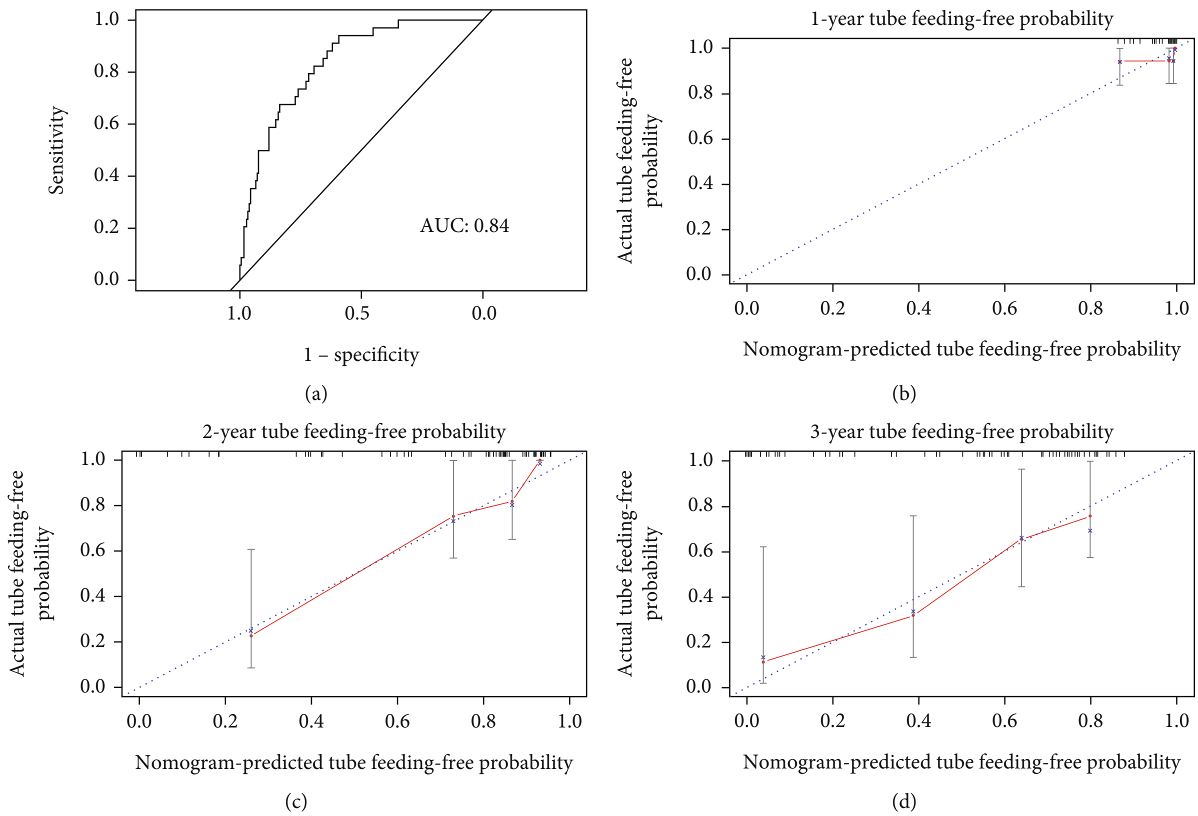

Figure 3: Receiver operating characteristic (ROC) curve and calibration curves of the nomogram. (a) The area under the curve (AUC) of using the nomogram to predict tube feeding-free probability, AUC = 0.84, which is considered ideal. (b–d) Calibration curves of 1-year, 2-year, and 3-year tube feeding-free prediction probability. The light blue line indicates the ideal reference line where predicted probabilities would match the observed prediction rates. The red dots are calculated by bootstrapping (resample: 1,000) and represent the performance of the nomogram.

onset were risk factors for gastrostomy indication [22]. Jackson-Tarlton et al. confirmed that the presence of swallowing problems, measured by swallowing score 3 or less of ALSFRS-R subscore (maximum 4 points), was strongly associated with the indication for percutaneous endoscopic gastrostomy (PEG) [23]. Similarly, in our study, we identified ALS patients with bulbar involvement at baseline as a sign of tube feeding. In addition, we found that the history of ischemic stroke was also associated with tube feeding, which needs more studies. But our study design differed from those former researches because we enrolled those patients who actually did the tube feeding procedure, while other studies included patients who simply had the indication for gastrostomy according to guidelines [22].

Based on the risk factors that were associated with the tube feeding procedure, we created the predictive nomogram integrated above multiple risk factors into a quantitative model, which could be helpful for physicians to predict the individualized probabilities of tube feeding for different patients. Moreover, our nomogram showed moderate discrimination and calibration using internal validation via bootstrap. Hence, this nomogram could help physicians better identify ALS patients who need early swallowing intervention and early healthcare recommendations.

Nowadays, guidelines recommend ALS patients with malnutrition (weight loss over 10%), mealtime duration over 45 minutes, and repeated aspirations to receive gastrostomy in order to keep sufficient nutrition [5, 8, 24, 25]. However, most ALS patients would be unwilling to accept the gastrostomy procedure, especially patients experiencing only mild dysphagia with weight loss and simply slow eating. The data from American patients showed that 48% of ALS patients met the criteria for enteral support, but less than half of those were suggested to have gastrostomy, and only 43% of those recommended patients finally received operation [26], indicating the low acceptance of gastrostomy in America. The rates of gastrostomy ranged from 11 to 60% across different countries for ALS patients but increased over the years because of guideline recommendations [27], while the rate of gastrostomy is lower in Chinese ALS patients (1.3%-27.10%) than in other countries according to a meta-analysis [28]. In China, ALS patients are more conservative in receiving invasive treatments and prefer to receive traditional Chinese medical treatment, and little evidence about gastrostomy was found in Chinese patients. In our study, we found that only 33.8% of ALS patients who were indicated for tube feeding eventually accepted gastrostomy. It is difficult to recommend Chinese patients who fit into the above criteria to receive gastrostomy in our clinical practice. The previous study showed that the latency time between gastrostomy recommendation and gastrostomy referral varied from less than 1 week to the longest 57 days. Considering gastrostomy and decision-

Table 3: The clinical characteristics of patients referred to tube feeding, stratified by the tube feeding at diagnosis or during follow-up.

Variables	Tube feeding acceptance No ($n = 37$) n (%) or mean (SD) or median (IQR)	Tube feeding acceptance Yes ($n = 34$) n (%) or mean (SD) or median (IQR)	Total ($n = 71$) n (%) or mean (SD) or median (IQR)	Statistics	p
At baseline					
Sex				χ^2	1
Male	21 (56.8)	19 (55.9)	40 (56.3)		
Female	16 (43.2)	15 (44.1)	31 (43.7)		
Familiar ALS	5 (13.5)	3 (8.8)	8 (11.3)	Fisher's exact test	0.712
Age of onset (y)	53.27 (11.81)	58.09 (12.37)	55.58 (12.24)	t-test	0.098
Death	12 (32.4)	14 (41.2)	26 (36.6)	χ^2	0.605
Site of disease onset				χ^2	0.586
Bulbar	14 (37.8)	16 (47.1)	30 (42.3)		
Spinal	23 (62.2)	18 (52.9)	41 (57.7)		
Time to diagnose (m)	12.00 (9.00, 18.00)	9.00 (6.25, 12.00)	11.00 (8.00, 14.50)	Mann–Whitney test	**0.016**
With loss of body weight at baseline	25 (67.6)	22 (64.7)	47 (66.2)	χ^2	0.997
BMI at baseline (kg/m^2)	21.24 (3.14)	21.15 (4.08)	21.20 (3.59)	t-test	0.911
Weight loss at baseline (kg)	3.00 (0.00, 5.00)	5.00 (0.00, 10.00)	5.00 (0.00, 10.00)	Mann–Whitney test	0.253
NBRI				Fisher's exact test	0.159
1	6 (16.2)	2 (5.9)	8 (11.3)		
2	8 (21.6)	5 (14.7)	13 (18.3)		
3	12 (32.4)	9 (26.5)	21 (29.6)		
4	10 (27.0)	18 (52.9)	28 (39.4)		
The involvement of different segments					
Bulbar involvement	30 (81.1)	32 (94.1)	62 (87.3)	Fisher's exact test	0.155
Upper limb involvement	28 (75.7)	28 (82.4)	56 (78.9)	χ^2	0.691
Lower limb involvement	25 (67.6)	30 (88.2)	55 (77.5)	χ^2	0.072
Respiratory involvement	15 (40.5)	21 (61.8)	36 (50.7)	χ^2	0.121
ALSFRS-R score	37.00 (31.00, 40.00]	31.00 (18.00, 36.75)	35.00 (27.50, 39.50)	Mann–Whitney test	**0.005**
Bulbar score	10.00 (6.00, 11.00)	5.50 (2.00, 10.00)	9.00 (5.00, 11.00)	Mann–Whitney test	**0.003**
Fine motor score	9.00 (6.00, 11.00)	7.00 (3.00, 9.00)	8.00 (4.00, 10.00)	Mann–Whitney test	**0.034**
Gross motor score	8.00 (6.00, 10.00)	5.00 (2.00, 8.75)	7.00 (3.00, 10.00)	Mann–Whitney test	0.094
Respiratory score	12.00 (11.00, 12.00)	11.00 (9.00, 12.00)	12.00 (10.00, 12.00)	Mann–Whitney test	**0.026**
ALSFRS-R slope	0.58 (0.35, 0.92)	0.84 (0.56, 1.37)	0.71 (0.45, 1.23)	Mann–Whitney test	**0.038**
Ischemic stroke	0 (0.0)	3 (8.8)	3 (4.2)	Fisher's exact test	0.105

Table 3: Continued.

Variables	Tube feeding acceptance No ($n = 37$) n (%) or mean (SD) or median (IQR)	Tube feeding acceptance Yes ($n = 34$) n (%) or mean (SD) or median (IQR)	Total ($n = 71$) n (%) or mean (SD) or median (IQR)	Statistics	p
During follow-up					
NIV routine users	12 (32.4)	20 (58.8)	32 (45.1)	χ^2	**0.046**
Dyspnea	21 (56.8)	26 (76.5)	47 (66.2)	χ^2	0.133
Dysphagia	30 (81.1)	24 (70.6)	54 (76.1)	χ^2	0.449
Past history					
Hyperlipidemia	1 (2.7)	4 (11.8)	5 (7.0)	Fisher's exact test	0.187
Hypertension	10 (27.0)	11 (32.4)	21 (29.6)	χ^2	0.817
Diabetes	2 (5.4)	1 (2.9)	3 (4.2)	Fisher's exact test	1
Drinking	12 (32.4)	12 (35.3)	24 (33.8)	χ^2	0.997
Smoking	15 (40.5)	13 (38.2)	28 (39.4)	χ^2	1
Depression	1 (2.7)	0 (0.0)	1 (1.4)	Fisher's exact test	1
Anxiety	0 (0.0)	1 (2.9)	1 (1.4)	Fisher's exact test	0.479
Malignancy	3 (8.1)	1 (2.9)	4 (5.6)	Fisher's exact test	0.615
Allergy	0 (0.0)	2 (5.9)	2 (2.8)	Fisher's exact test	0.226
Exposure of toxic substances	5 (13.5)	6 (17.6)	11 (15.5)	χ^2	0.879
Trauma	7 (18.9)	9 (26.5)	16 (22.5)	χ^2	0.634
Surgical history	14 (37.8)	12 (36.4)	26 (37.1)	χ^2	1

Tube feeding consists of gastrostomy and nasogastric tube feeding. Patients who received tube feeding had a shorter time from disease onset to diagnosis, lower ALSFRS-R score, lower bulbar score, lower fine motor score, and lower respiratory score than patients without swallowing intervention at baseline. During the follow-up, patients who received tube feeding were more likely to receive NIV support than those without. However, ALS patients with past history at diagnosis (such as hyperlipidemia, hypertension, diabetes, drinking, smoking, depression, anxiety, malignancy, allergy, exposure of toxic substances, trauma, and surgical history) had no difference in the acceptance of tube feeding. Familiar ALS patients were not more accepting of tube feeding than others. The mortality rate of patients with tube feeding was similar to those without tube feeding. Note: ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale revised; BMI: body mass index; y: year; m: month; kg: kilogram; NIV: noninvasive ventilation; NBRI: body regions involved; *n*: number; *p*: probability. In bold: *p* value < 0.05.

making is a complicated and multifaceted process for ALS patients [29]. With early identification of ALS patients who had the higher risk for gastrostomy, providing on-time recommendation of gastrostomy and appropriate healthcare education to these ALS patients and their caregivers could improve the acceptability of gastrostomy and avoid unnecessary delay. And the nomogram may provide help in this process.

Some observational studies showed that gastrostomy was beneficial to expend ALS patients' lifetime, but the survival benefit from gastrostomy still cannot be definitively proven [30]. Thus, we then assessed the survival of patients in our study and found that gastrostomy or NGT insertion had no harmful impact on patients' survival, which was similar in the French cohort [22]. The reason might be that our follow-up was short and only 36.6% of our ALS patients with gastrostomy indication reached the end-event of death.

Several studies concluded differently that gastrostomy was harmful to the survival of patients [31, 32]. In these studies, the methods of gastrostomy procedure might be varied in ALS patients, including PEG, radiologically inserted gastrostomy (RIG), and per-oral image-guided gastrostomy (PIG). Although the ProGas study failed to show a significant difference in survival and procedural complications between the three methods, RIG is less invasive than PEG and safer in ALS patients with respiratory dysfunction (FVC < 50%), as it employs a smaller tube and usually requires less sedation [33]. In our clinic, ALS patients primarily receive RIG, which may partially explain why our ALS patients might benefit from gastrostomy procedures, though without significant difference. But we did not analyze the proportion of this type of gastrostomy in our patients. Therefore, gastrostomy might be beneficial for selected

Table 4: The clinical characteristics of ALS patients referred to tube feeding, stratified by survival.

Variables	Death: No ($n = 45$) n (%) or mean (SD) or median (IQR)	Death: Yes ($n = 26$) n (%) or mean (SD) or median (IQR)	Total ($n = 71$) n (%) or mean (SD) or median (IQR)	Statistics	p value
At baseline					
Sex				χ^2	0.06
Male	21 (46.7)	19 (73.1)	40 (56.3)		
Female	24 (53.3)	7 (26.9)	31 (43.7)		
Age of onset	54.36 (13.42)	57.69 (9.75)	55.58 (12.24)	t-test	0.27
Site of disease onset				χ^2	0.21
Bulbar	16 (35.6)	14 (53.8)	30 (42.3)		
Spinal	29 (64.4)	12 (46.2)	41 (57.7)		
BMI (kg/m^2)	22.00 (19.00, 24.00)	20.00 (18.00, 23.00)	21.00 (19.00, 24.00)	Mann–Whitney test	0.08
Weight loss (%)	27 (60.0)	20 (76.9)	47 (66.2)	χ^2	0.23
Weight loss (kg)	3.00 (0.00, 8.00)	5.50 (3.00, 12.25)	5.00 (0.00, 10.00)	Mann–Whitney test	**0.04**
Time to diagnose (months)	12.00 (8.00, 14.00)	9.00 (6.00, 14.75)	11.00 (8.00, 14.50)	Mann–Whitney test	0.24
Bulbar score	10.00 (5.00, 11.00)	6.00 (3.00, 9.00)	9.00 (5.00, 11.00)	Mann–Whitney test	**0.01**
Gross motor score	8.00 (4.00, 9.00)	7.00 (4.25, 10.75)	8.00 (4.00, 10.00)	Mann–Whitney test	0.93
Fine motor score	7.00 (2.00, 9.00)	7.00 (3.25, 10.00)	7.00 (3.00, 10.00)	Mann–Whitney test	0.61
Respiratory score	12.00 (11.00, 12.00)	11.50 (9.25, 12.00)	12.00 (10.00, 12.00)	Mann–Whitney test	0.54
NBRI				Fisher's exact test	1
1	5 (11.1)	3 (11.5)	8 (11.3)		
2	8 (17.8)	5 (19.2)	13 (18.3)		
3	13 (28.9)	8 (30.8)	21 (29.6)		
4	18 (40.0)	10 (38.5)	28 (39.4)		
ALSFRS-R score	35.00 (29.00, 40.00)	34.00 (20.00, 39.00)	35.00 (27.50, 39.50)	Mann–Whitney test	0.33
ALSFRS-R slope	0.68 (0.38, 0.92)	0.98 (0.54, 1.72)	0.71 (0.45, 1.23)	Mann–Whitney test	**0.01**
History of ischemic stroke	0 (0.0)	3 (11.5)	3 (4.2)	Fisher's exact test	**0.04**
At follow-up					
NIV routine users	21 (46.7)	11 (42.3)	32 (45.1)	χ^2	0.91
Dyspnea	30 (66.7)	17 (65.4)	47 (66.2)		1

At baseline, the mortality rate of ALS patients was higher in those with more weight loss (kg), lower bulbar score, higher ALSFRS-R slope, and history of ischemic stroke. Note: ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale revised; NBRI: body regions involved; BMI: body mass index; NIV: noninvasive ventilation; aHR: adjusted hazard ratio; cHR: crude hazard ratio; y: year; m: month; kg: kilogram; 95% CI: 95% confidence interval. In bold: p value < 0.05.

ALS patients with the right timing and suitable surgery type, which needs more studies.

We acknowledge the limitations of this study. Firstly, we only validated our predictive model using internal validation via bootstrap. More external validations are needed to be conducted in the future study. Meanwhile, we did not know whether this predictive model could be generalizable beyond populations of Chinese ALS patients. Secondly, we did not distinguish the different methods of gastrostomy and their impact on survival. Additionally, our sample size was small. Thus, physicians need to use this predictive model more cautiously in clinical applications.

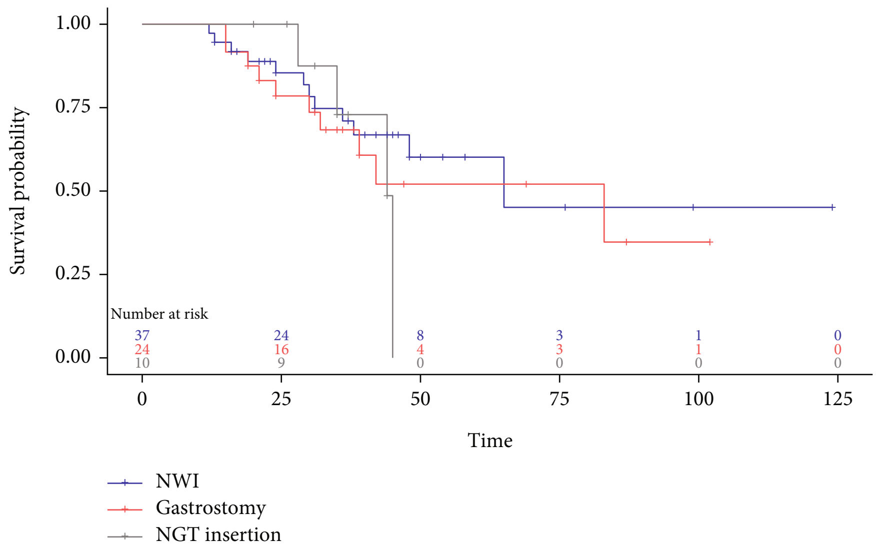

Figure 4: The Kaplan-Meier survival curves for gastrostomy, NGT, and NWI groups. Subsequent Cox proportional hazard analysis suggested that the method of gastrostomy or NGT insertion was not significantly associated with survival. Note: NWI: nonswallowing intervention; NGT: nasogastric tube.

Table 5: Factors associated with the ALS patient's survival in univariate and multivariate analysis with the Cox regression analysis ($N = 71$).

Variables	cHR (95% CI)	p value	aHR (95% CI)	p value
Sex	**2.92 (1.21-7.01)**	**0.02**	**3.74 (1.34-10.44)**	**0.01**
Time to diagnose (m)	0.95 (0.9-1.01)	0.1	0.96 (0.89-1.04)	0.32
Weight loss (%)[a]	**2.66 (1.06-6.69)**	**0.04**	0.68 (0.15-3.11)	0.62
Weight loss at baseline (kg)[a]	**1.07 (1.02-1.13)**	**0.01**	1.06 (0.94-1.19)	0.36
BMI (kg/m^2)[a]	0.9 (0.8-1)	0.06	0.86 (0.72-1.03)	0.1
Bulbar onset	2.08 (0.95-4.55)	0.07	**4.89 (1.07-22.36)**	**0.04**
Bulbar score[a]	**0.91 (0.83-1)**	**0.05**	1.13 (0.9-1.41)	0.3
Fine motor score[a]	1.1 (0.99-1.22)	0.07	**1.25 (1.06-1.48)**	**0.01**
ALSFRS-R slope[a]	**5.19 (2.84-9.48)**	**<0.001**	**9.2 (3.74-22.64)**	**<0.001**
Depression[a]	**16.84 (1.88-150.68)**	**0.01**	10.53 (0.69-160.85)	0.09
History of ischemic stroke	**14.61 (3.68-58.05)**	**<0.001**	**6.34 (1.27-31.63)**	**0.03**

Factors associated with survival with p value lower than 0.1 using the univariate Cox regression were enrolled in the multivariate Cox regression analysis. Male gender, high ALSFRS-R slope, high fine motor score, history of ischemic stroke, and bulbar onset were identified as independent risk factors of death using the multivariate Cox regression. Note: ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale revised; BMI: body mass index; aHR: adjusted hazard ratio; cHR: crude hazard ratio; y: year; m: month; kg: kilogram; 95% CI: 95% confidence interval; a: at baseline. In bold: p value < 0.05.

5. Conclusions

Our findings demonstrate that rapid disease progression, low bulbar score, bulbar involvement, and history of ischemic stroke were associated with early tube feeding. And we create a nomogram to provide individualized timing of tube feeding for ALS patients. More studies are needed to determine the feasibility of this predictive model. Last but not least, our study shows that gastrostomy would not accelerate the disease progression and might positively affect ALS patients' survival but without significant difference.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Disclosure

The funding source had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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