Risk Factors and Outcomes for Refeeding Syndrome in Acute Ischemic Stroke Patients

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Research Article

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Abstract

**Background** Acute ischemic stroke (AIS) is more likely to develop refeeding syndrome (RFS) due to increased need for nutritional support when suffering dysfunction of consciousness and deglutition after stroke. This study aims to evaluate the occurrence, risk factors and outcomes of RFS in AIS patients.

**Methods** This retrospective observational study, using the prospective stroke database from our hospital, included all consecutive AIS patients who received parenteral or enteral nutrition for more than 72 hours from January 1, 2019 to December 31, 2021. RFS was defined as occurrence of new onset hypophosphatemia within 72 hours after refeeding. Multiple logistic regression analysis was conducted to evaluate risk factors for RFS and relationship between RFS and 3-month modified Rankin Scale (mRS) score and 6-month mortality.

**Results** Of 1038 patients were included in the study, 154 patients (14.8 %) developed RFS. We found that baseline National Institutes of Health Stroke Scale (NIHSS), nutritional risk screening (NRS) 2002, albumin < 30g/L and body mass index (BMI) < 18.5 kg/m$^2$ were risk factors for RFS in AIS patients. Moreover, Patients in RFS group had lower 7-day NIHSS and RFS was independently associated with a 3-month mRS score of > 2 and 6-month mortality.

**Conclusion** RFS is common in AIS patients and higher baseline NIHSS, higher NRS 2002 score, albumin < 30g/L and BMI < 18.5 kg/m$^2$ significantly increased the risk of RFS. Occurrence of RFS was significantly associated with higher 3-month mRS score and 6-month mortality.

Introduction

Refeeding syndrome (RFS) is usually defined as the fluid and electrolyte disturbance during refeeding after long-term malnutrition or starving, which can lead to failure of respiratory, cardiac, hepatic, hematological, neurologic and death. RFS can be induced by either enteral or parenteral nutrition support [1]. Acute ischemic stroke (AIS) patients are often subjected to malnutrition and require nutrition support due to dysfunction of deglutition, cognitive, consciousness and increased metabolic needs [2, 3]. Thus, AIS patients may be more likely to develop RFS. Moreover, RFS has been reported to be significantly associated with poor prognosis by increasing risk of mortality and continuing disability [4, 5]. Hence, it is of great significance to recognize high-risk patients of RFS and conduct strict nutritional management for AIS patients.

Hypophosphatemia is the main physiological characteristic for RFS and diagnostic criteria for RFS was commonly defined as new onset of hypophosphatemia with a fall of phosphate levels >0.16mmol/L to below 0.65mmol/L [6]. Incidence of RFS varies in different population and different feeding approaches. Based on the aforementioned definition, a recently randomized clinical trial found an incident of 34% in critically ill, invasive mechanically ventilated patients admitted for >7 days to a medical surgical intensive care unit (ICU) [7]. Another large retrospective cohort study conducted in our contrary found an incident of
17.1% in neurocritically ill patients [8]. However, incident of RFS in AIS patients were little reported and remain elucidated. Low body mass index (BMI), significant weight loss in the last 3-6 months, fasting or little food intake for more than 5 days, presence of electrolyte disturbance before refeeding and alcohol abuse were considered as risk factors for RFS in critically ill patients according to Guidelines for nutrition management of The European Society for Clinical Nutrition and Metabolism (ESPEN) [2]. Also, There are reports shows that age, low albumin, high nutritional intake, low insulin like growth factor-1, and enteral feedings should be taken into account for different populations [9, 10]. Another study showed that high malnutrition universal screening tool (MUST) and sequential organ failure assessment (SOFA) may increase risk of RFS in neurocritically ill patients and occurrence of RFS also acts as an independent risk factors for 6-month mortality [2, 8, 11, 12]. However, although AIS patients are high risk group for RFS, few investigations focus on AIS population to evaluate the incidence and risk factors of RFS. Relationship of RFS and AIS outcomes were also unclear.

Here in this retrospective study, we aim to investigate incident and risk factors of RFS in AIS patients. Whether occurrence of RFS could negatively influence early and long-term outcomes of AIS was also assessed in this study.

**Methods**

**Patients and study design**

We retrospectively reviewed consecutive patients diagnosed with AIS requiring enteral or parental nutritional support, admitted to stroke unit of Guangdong Hospital of Traditional Chinese and Western Medicine between January 1, 2019 and December 31, 2021. The inclusion criteria were as following: (1) acute ischemic stroke was demonstrated by diffusion-weighted imaging (DWI); (2) intracranial hemorrhage (ICH) was excluded by non-contrast computed tomograph (CT); (3) receiving enteral or parental nutritional support for > 72 hours; (4) had serum phosphate records before refeeding and at 72±12 h after refeeding. Patients were excluded if they met one of the following criteria: (1) had incomplete data on nutrition provision; (2) were aged > 85 or < 18 years; (3) had serum phosphate < 0.65 mmol/L at admission; (4) were lost to follow-up; (5) had end-stage malignant diseases; (6) had complications for diabetic ketoacidosis or (7) had recent parathyroidectomy or were receiving renal replacement therapy, using phosphate binders, or undergoing the therapeutic hypothermia.

This is a single-center, observational, retrospective cohort study using prospective collected data from our stroke database. Informed consent from patients or review board was waived because of its observational and retrospective properties.

**Management For Ais Patients**
All AIS patients admitted to our unit were treated in accordance with Chinese guidelines. Routine blood examinations, including blood routine tests, electrolytes, liver and kidney function, coagulation, troponin and C-reactive protein (CRP), etc, were conducted at admission and reviewed selectively according to abnormal initial results. Serum phosphate was required to be reviewed at 72 hours after refeeding to early identify possible RFS. We performed strict nutrition management for each patient. NRS 2002 and MUST scores were conducted for all AIS patients to evaluate condition of nutrition at admission. Patients who are unable to eat on their own would receive individual nutritional support, mostly by enteral nutrition support, and total calorics per day were calculated and recorded regularly by professional nutritionist. Patients would receive repeated evaluation of nutritional conditions during hospitalization to adjust nutrition strategy in time.

**Diagnosis Of Rfs And Data Collection**

RFS was defined as new onset of hypophosphatemia within 72 hours after refeeding. Hypophosphatemia was defined as a drop of serum phosphate more than 0.16 mmol/L from admission to below 0.65 mmol/L. Based on this criterion, all included patients were divided into two groups, the RFS group and the non-RFS group. The following data were collected: age, gender, diabetes, coronary artery disease (CAD), previous stroke, smoking, serum glucose, blood pressure, blood electrolytes which including phosphate, potassium, sodium and magnesium, albumin, CRP, serum creatinine, total calorie per day for the first three days, baseline National Institutes of Health Stroke Scale (NIHSS) and mRS, modified Rankin Scale (mRS) at admission, nutritional risk screening (NRS) 2002 and MUST score at admission. 3-month mRS and 6-month mortality were evaluated by neurologists on outpatient appointment or by telephone follow-up.

**Statistical analysis**

Continuous variables were described as mean ± standard deviations or medians (and interquartile ranges) and categorical variables as number (percentage). The Kolmogorov–Smirnov test was used to test the normality of the data. Where quantitative data did not show a normal distribution, the Mann–Whitney rank sum test was used for group comparisons. Continuous, whereas categorical variables were compared with Fisher exact test or the $\chi^2$ test. Candidate variables that had a $P$ value less than 0.05 in the univariate analysis were drawn into multivariable logistic regression models to evaluate independent predictors for RFS. Ordinal logistic regression analysis was also conducted to evaluate the association between RFS and outcomes of AIS. An $P$ value of 0.05 was considered statistically significant. All analysis was performed using SPSS 22.0 statistical software.

**Results**

**Patients characteristics**
Of 1038 patients diagnosed with AIS and received nutritional support enrolled in the study, 154 patients developed RFS (14.8%). 684 patients were men (65.9%) and the average age was 64 years old in the population. The flow diagram of the analyzed cohort was shown in Figure 1. There were no intergroup significant differences in the demographic characteristics and history diseases (Table 1). Baseline NIHSS score (median, 10 versus 6; \( P<0.001 \)), MUST (median, 2 versus 1; \( P=0.012 \)), NRS 2002 (median, 3 versus 4; \( P<0.001 \)), and diastolic blood pressure (DBP) (85.8 ±11.3 versus 83.6 ±10.1; \( P=0.024 \)) were significantly higher in the RFS group than the non-RFS group. For baseline blood tests, hemoglobin (median, 130 versus 120; \( P=0.035 \)) and albumin (median, 35 versus 39; \( P=0.041 \)) displayed lower and CRP (median, 10 versus 7; \( P=0.001 \)) higher in the RFS group than non-RFS group. Patients in the RFS group received more calorie than that in the non-RFS group at the first day.
Table 1
Baseline Characteristics of patients

| Characteristics                  | RFS Group (n=154) | Non-RFS Group (n=884) | P value |
|---------------------------------|-------------------|-----------------------|---------|
| Demographics                    |                   |                       |         |
| Age, y, mean±SD                 | 65.2 ± 10.6       | 63.9 ± 12.4           | 0.064   |
| Gender, male, n (%)             | 109 (70.8)        | 575 (65.0)            | 0.166   |
| Medical History, n (%)          |                   |                       |         |
| Hypertension                    | 97 (63.0)         | 556 (62.9)            | 0.983   |
| Diabetes                        | 51 (33.1)         | 223 (25.2)            | 0.040*  |
| CAD                             | 29 (18.8)         | 133 (15.0)            | 0.232   |
| Previous stroke or TIA          | 28 (18.1)         | 221 (25.0)            | 0.067   |
| Smoking                         | 101 (65.6)        | 568 (64.2)            | 0.750   |
| On admission                    |                   |                       |         |
| SBP, mmHg, mean±SD              | 154.2 ± 15.9      | 153.9 ± 18.6          | 0.833   |
| DBP, mmHg, mean±SD              | 85.8 ± 11.3       | 83.6 ± 10.1           | 0.024*  |
| Serum glucose, mmol/L, mean±SD | 6.9 ± 2.4         | 7.2 ± 1.7             | 0.137   |
| Baseline NIHSS, median (IQR)    | 10 (4-13)         | 6 (3-9)               | < 0.001*|
| Baseline mRS, median (IQR)      | 3 (2-4)           | 3 (1-3)               | 0.056   |
| NRS 2002, median (IQR)          | 3 (3-5)           | 2 (1-3)               | < 0.001*|
| MUST, median (IQR)              | 2 (2-2)           | 1 (0-1)               | 0.012   |
| BMI, kg/m², median (IQR)        | 18.9 (17.5-20.9)  | 20.4 (19.6-23.5)      | < 0.001*|
| Blood Test                      |                   |                       |         |
| Hemoglobin, g/L, median (IQR)   | 130 (101-139)     | 140 (120-149)         | 0.035*  |
| Albumin, g/L median (IQR)       | 35 (27-39)        | 39 (36-42)            | 0.041*  |
| Creatinine, µmol/L, median (IQR)| 76.4 (56.4-89.5)  | 80.2 (78.6-94.5)      | 0.067   |
| CRP, mg/L, median (IQR)         | 10 (8-19)         | 7 (6-15)              | < 0.001*|
| BNP, pg/mL, median (IQR)        | 56 (34-94)        | 64 (45-95)            | 0.995   |
| Characteristics                           | RFS Group (n=154) | Non-RFS Group (n=884) | P value |
|------------------------------------------|-------------------|-----------------------|---------|
| Phosphate, mmol/L, median (IQR)          | 1.03 (0.72-1.13)  | 1.05 (0.85-1.21)      | 0.189   |
| Potassium, mmol/L, median (IQR)          | 3.91 (3.68-5.29)  | 4.25 (3.10-5.34)      | 0.306   |
| Sodium, mmol/L, median (IQR)             | 141 (137-142)     | 139 (136-143)         | 0.978   |
| Magnesium, mmol/L, median (IQR)          | 0.85 (0.73-0.94)  | 0.84 (0.72-0.95)      | 0.224   |
| Caloric intakes within the first 72 hours|                   |                       |         |
| Day 1, Kcal, median, (IQR)               | 550 (500-600)     | 500 (450-550)         | 0.034*  |
| Day 2, Kcal, median, (IQR)               | 950 (950-1200)    | 1000 (950-1250)       | 0.463   |
| Day 3, Kcal, median, (IQR)               | 1450 (1400-1600)  | 1500 (1500-1600)      | 0.443   |
| Outcomes                                 |                   |                       |         |
| 7-day NIHSS changes, median, (IQR)       | 1 (0-3)           | 2 (1-4)               | 0.004   |
| 3-month mRS, median, (IQR)               | 3 (2-4)           | 2 (1-3)               | < 0.001*|
| 6-month mortality, n (%)                 | 3 (1.9)           | 5 (0.6)               | 0.010   |

**Risk Factors For Rfs In Ais Patients**

In multivariable logistic analysis, NIHSS score, mRS score and calorie intake at second day were included in Model A and NIHSS (OR, 2.123; 95% CI, 1.754-3.014; P=0.024) and NRS 2002 (OR, 1.987; 95% CI, 1.528-3.446; P< 0.001) were found significantly associated with occurrence of RFS in AIS patients (Table 2). In Model B, which included DBP, hemoglobin, albumin, CRP, diabetes and BMI, albumin < 30 g/L (compared to ≥ 30 g/L; OR, 1.594; 95% CI, 1.328-2.416; P= 0.025) and BMI <18.5 kg/m² (compared to ≥18.5 kg/m²; OR, 1.346; 95% CI, 1.245-1.569; P= 0.045) were risk factors for RFS (Table 2). MUST were not included in the Model A because of its collinearity with NRS 2002.
Table 2
Risk factors for RFS in AIS patients

| Risk factors       | OR (95% CI)     | P value |
|--------------------|-----------------|---------|
| **Model A**        |                 |         |
| Day 1 caloric intake | 1.057 (0.984-1.173) | 0.541   |
| NIHSS              | 2.123 (1.754-3.014) | 0.024   |
| NRS 2002<sup>a</sup> | 1.987 (1.528-3.446) | < 0.001* |
| **Model B**        |                 |         |
| Albumin < 30g/L    | 1.594 (1.328-2.416) | 0.025*  |
| BMI < 18.5         | 1.346 (1.245-1.569) | 0.045*  |
| DBP > 90 mmHg      | 1.138 (0.894-1.226) | 0.137   |
| CRP > 10 mg/L      | 1.046 (0.556-1.109) | 0.754   |
| Diabetes           | 1.036 (0.826-1.124) | 0.256   |
| Anemia             | 0.789 (0.984-1.173) | 0.541   |

Influence Of RFS On AIS Patients

RFS group patients had lower 7-day NIHSS promotion than that in the non-RFS group (median, 1 versus 2; P= 0.004) (Table 1). During the follow-up, 3-month mRS (median, 3 versus 2; P< 0.001) and 6-month mortality (1.9% versus 0.6%; p < 0.001) were significantly higher in the RFS group than the non-RFS group (Table 1 and Figure 2). Ordinal logistic regression analysis, after adjusting confounders including age and baseline NIHSS, showed a significant association between RFS and both the mRS score of > 2 at 3 months (OR, 1.794; 95% CI, 1.378-2.564; P= 0.016) and mortality at 6 months (OR, 2.561; 95% CI, 2.245-3.649; P< 0.001) (Table 3).

Table 3
Outcomes of RFS in AIS patients

| Outcomes          | OR       | 95% CI      | P Value |
|-------------------|----------|-------------|---------|
| 3-month mRS       | 1.794    | 1.378-2.564 | 0.016*  |
| 6-month mortality | 2.561    | 2.245-3.649 | < 0.001* |

Discussion
RFS has grown to a research hotspot of multiple subjects in view of its prevalence and close relationship with disease outcomes. However, incidence and risk factors of RFS in AIS patients remains unclear and the its influence on stroke outcomes were rarely reported. Here in this study, we take the lead to specially focus on RFS in AIS population and found that there were 14.8% of AIS patients developing RFS. High NRS 2002 and NIHSS score, as well as albumin < 30 g/L and BMI < 18.5 kg/m$^2$ were risk factors for RFS in AIS patients. Also, results showed that RFS increased risk of poorer stroke outcomes with higher proportion of 3-month mRS of >2 and 6-month mortality.

The incidence of RFS in AIS patients in this current study was lower than other population in previous studies. By using the same definition of RFS, the incidence of RFS ranges from 34–45% in ICU patients as described by Olthof et al. and Hoffmann et al $^{[7, 13]}$. However, with different definition, Flesher et al. found an even higher incidence of 80% in critically ill patients$^{[14]}$. Thus, different definition and population may induce adverse occurrence rate of RFS. Our study included AIS patients, partly of which were mild stroke with better conditions of nutrition. Moreover, since 2019 when ESPEN guidelines for RFS prevention and treatment were public $^{[2]}$, our stroke unit performed a calorie restriction combined with supplies of Centrum multi element during the first three days to prevent electrolyte disturbance for patients with high risk of malnutrition, which may decrease development of RFS and thus explain why we have lower incidence of RFS in AIS patients. Further studies with multi-subgroup analysis based on stroke severity and stroke subtypes are required to clarify the incidence of RFS in AIS patients.

Many screening tools reflecting disease severity and nutrition status were found to be associated with development of RFS in critically ill patients, including SOFA, Acute Physiology and Chronic Health Evaluation II (APACHE II) and MUST $^{[8]}$. In our study, we included multiple scoring systems and found that high NIHSS and NRS 2002 increased risk of RFS in AIS patients. NIHSS score is a universally accepted standardization to evaluate severity of acute ischemic stroke and higher NIHSS score indicates more extensive neurologic deficits, especially impairment of cognitive, consciousness and swallowing, and thus lead to metabolic disturbance $^{[15]}$. In addition, NRS 2002 was suspected to be collinearity with MUST in previous study, which is further demonstrated in our study due to its comparative predictive value of RFS $^{[8]}$. In terms of bio-metabolic markers, we identified albumin < 30g/L and BMI < 18.5 kg/m$^2$ as risk factors for RFS in AIS patients. Hypoalbuminemia is also reported to be relative to RFS in ICU patients because of its reflection of systemic nutritional condition and immune to variety of diseases $^{[16]}$. Besides, low magnesium and low insulin-like growth factor-1 (ILGF-1) were considered as risk factors for RFS in ICU patients $^{[17, 18]}$, which was not investigated in our study. We did not find a significant relationship of CRP with RFS. We assumed that high level of CRP was attached to RFS because the higher CRP manifests systemic inflammatory status, which may induce increased nutritional requirement and lead to malnutrition $^{[16]}$. On this context, nutritional support, especially enteral support, may potentially cause acquired hypophosphatemia. Nevertheless, results in our study were in contrary to the hypothesis and the poor accuracy of CRP to recognize systemic inflammation may contributed to this result $^{[19]}$. It is worthy to further assess whether other AIS-associated inflammatory factors or combination of CRP with other biomarkers is more sensitive to predict RFS in AIS.
The sensitivity and accuracy of National Institute for Health and Care Excellence (NICE) criteria to predict RFS were only 78% and 38% respectively as reported in a previous study [20]. A modified NICE criteria described by Friedli, which includes multiple demonstrated risk factors, such as BMI, large loss of weight, drug use of acid-inhibitor and so on, was also reported to have low sensitivity of RFS prediction [21]. Hence, it is urgent to recognize relative risk factors for RFS and establish a comprehensive screening system reflecting both disease severity and nutritional status to facilitate RFS prediction.

With regard to outcomes of RFS on AIS patients, RFS was detected to be an independent risk factor for 6-month mortality, which was concordant with a recent study focusing on NCU patients [8]. Also, results showed that RFS was significantly associated with a 3-month mRS of > 2. Poorer stroke outcomes may be attributed to hypophosphatemia that may directly induce secondary neuromuscular injury or aggravating neurologic ischemia through decreasing oxygen delivery of red blood cell [22–24]. Moreover, hypophosphatemia would lead to respiratory muscle dysfunction and potentially result to respiratory failure [25, 26]. All these pathologic changes ultimately lead to continuous neurologic disability and higher risk of death.

The major strength of this study is that it is the first investigation to focus on RFS in AIS population and included multiple biochemical indicators and scoring systems to evaluate risk factors and outcomes of RFS. Our results may provide reliable reference for nutritional management. There are also limitations. First, it is a retrospective, single-center study and excluded those lost to follow-up or without serum phosphate at 72 hours. We could not deny the selection bias and residual confounding. However, our prospective collected database may partly compensate for the retrospective nature. Second, part of patients may develop RFS beyond 72 hours and were divided into the non-RFS group, which may underestimate the incidence of RFS. Third, due to the small number of RFS patients, multi-subgroup analysis on diverse stroke severity and stroke subtypes were not conducted to further clarify the prevalence and risk factors of RFS in AIS patients. A prospective, randomized cohort study was required to further verify results in this current study.

**Conclusion**

In conclusion, the present study suggests a high morbidity of RFS in AIS patients and high NRS 2002 score and NIHSS, as well as lower albumin and BMI were risk factors for RFS. Occurrence of RFS increase the risk of poorer neurologic outcome at 3-month and death at 6 months.

**Abbreviations**

NIHSS
National Institutes of Health Stroke Scale
NRS 2002
nutritional risk screening
mRS
Declarations

Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding authors (HS) on reasonable request.

Ethics approval and consent to participate

all methods included in the current study were carried out in accordance with relevant guidelines and regulations. All experimental protocols were approved by the medical ethics committee of the Guangdong Hospital of Integrated Traditional Chinese and Western Medicine, Affiliated hospital of Traditional Chinese University of Guangzhou. Written informed consents were obtained from all patients or their legal guardians.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.
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Authors' contributions

SC designed the study and wrote the manuscript. DC and JH helped to collect the clinical data. RC and YL performed the statistical analysis. LZ and HS revised and approved the paper.

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**Figures**
Figure 1

Selection process of patients.
Figure 2

3-month mRS of AIS patients in RFS group and non-RFS group.

Supplementary Files

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