

The Diagnostic Criteria of Refeeding Syndrome in Critically Ill Patients from four Chinese Hospitals: A Multicenter Prospective Study

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Research

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Abstract

Background: Refeeding syndrome (RFS) is a group of metabolic disorders associated with refeeding after starvation. However, the diagnostic criteria of RFS are highly heterogeneous. This study aimed to identify the best diagnostic criteria of RFS in critically ill patients.

Methods: A multicenter, parallel, prospective trial enrolled patients (≥ 18 years) with mechanical ventilation for more than 3 days. RFS, defined as new-onset hypophosphatemia (< 0.87 mmol/L) within 72 h after feeding and a decreased concentration of serum phosphate of more than 30%, from four hospital ICU of Zhejiang provinces in China. The primary endpoint was the 28-day mortality.

Results:

Between May 1, 2019 and April 30, 2020, 312 patients were enrolled. Of these, 302 patients were included and completed the trial. Except for APACHE II, there were no significant differences in age, gender, admission type, diagnosis, furosemide application, and hormone application. In the RFS2 and RFS3 groups, the APACHE II score was significantly higher than the non-RFS group ($p=0.009$ and $p=0.01$, respectively). In the nutritional baseline data, there were no significant differences between the groups in the PNI index, time to start of nutrition treatment, percentage of start nutrition within 48 hours, parenteral nutrition, feeding intolerance, and caloric intake and protein intake within first week. The NRS2002 score in group 2 and 3 was higher than the non-RFS group ($p<0.001$ and $p=0.001$, respectively). Moreover, the BMI index in group 3 was lower than the non-RFS group ($p=0.001$). Furthermore, the 28-day mortality increased in group 2 compared with the non-RFS group. The length of hospital stay in group 3 was significantly longer than that in the non-RFS group ($p=0.008$). More importantly, according to the preliminary RFS2 screening criteria, patients were further divided into patients with modified RFS and modified non-RFS. The nosocomial infection rate and 28- or 90-day mortality in the modified RFS group were higher than those of the modified non-RFS group ($p=0.006$ and $p=0.02$, respectively).

Conclusions: The optimal criterion of RFS was a decrease in serum phosphate level of 0.65 mmol/L and below, and a reduction of greater than 0.16 mmol/L within 72 h after starting nutritional support.

Trial registration: ClinicalTrials.gov database, NCT04005300. Registered 1 July 2019, <https://clinicaltrials.gov/ct2/show/NCT04005300>

1. Background

Refeeding syndrome (RFS) is a group of metabolic disorders associated with refeeding[1]. Serum hypophosphatemia is a typical clinical sign of RFS, and other metabolic disturbances, such as hypokalemia, thiamine deficiency, and fluid overload. RFS is not rare. It is common in short-term fasting patients, especially critically ill patients[2]. Consequently, patients who are at high nutritional risk or severely malnourished should be advanced toward improvement, while monitoring for RFS[3].

Clinical standards consensus relating to refeeding hypophosphatemia is still lacking. Besides, RFS mortality and morbidity during critical illnesses have not been well-studied because of variable definitions, clinicians' unfamiliarity with RFS, and the complexities between acute illnesses and RFS. Moreover, some studies included both clinical and electrolyte abnormalities in the diagnosis of RFS, while in other studies, electrolyte disturbance was the only diagnostic criterion[4, 5]. This study aimed to discuss the diagnostic criteria of RFS.

2. Methods

2.1 Study design

We performed a multicenter, single-blind prospective clinical trial in 4 hospital ICU from Zhejiang provinces in China. Ethical approval was granted by the Institutional Review Board (NO: I2019001223). The study protocol was registered at <http://www.clinicaltrials.gov> (NCT04005300).

Adult patients, aged 18-year-old and over, requiring mechanical ventilation, from 4 ICU were included in the study from May 1, 2019, to April 30, 2020. All the patients were admitted for nutritional treatment for more than 3 days and their serum phosphate level was monitored regularly. Patients were excluded from the study if they had parathyroidectomy or received renal replacement therapy or phosphate binders. Readmitted patients were also excluded. The patient's nutritional characteristics were recorded, including age, gender, body mass index (BMI), nutrition risk score 2002(NRS2002), acute physiology and chronic health evaluation II (APACHEII)score, baseline blood tests, and the time before the commencement of nutritional treatment in ICU.

Based on the different serum phosphate measurements[6], three diagnostic criteria of RFS were used in this study. Criterion 1 (RFS1):serum phosphate levels between 0.65 and 0.87 mmol/L and the rate of decline was greater than 30% within 72 h after starting nutritional support).Criterion 2 (RFS2):serum phosphate levels between 0.32 and 0.65 mmol/L and the rate of change was greater than 0.16 mmol/L within 72 h after starting nutritional support).Criterion 3 (RFS3):serum phosphate levels below 0.32 mmol/L within 72 h after feeding) (Fig. 1).

Based on the result of this study, we further combined RFS2 and RFS3 and referred to as the modified RFS group. Moreover, RFS1 and non-RFS were combined into a modified non-RFS group.

2.2 Clinical Analyses

Daily caloric intake of the patients including enteral or parenteral nutrition, propofol, and sodium citrate, was recorded during the first week after enrollment. All patients who were finally included in the study were analyzed.

2.3 Outcome

The primary endpoint was the 28-day mortality. The secondary endpoints included the 90-day mortality, nosocomial infections, AKI, LOS of ICU and/or hospital, and the duration of mechanical ventilation (MV) in days.

2.4 Data Collection And Protection

All data were obtained from the four hospital databases, verified by two different researchers manually, and stored in a hospital computer.

2.5 Statistical Analysis

Quantitative data were expressed as mean \pm standard deviation (SD), which were dichotomized or categorized if necessary. Categorical and binary variables were reported as frequency or percentage. The equality of variances was assessed by Levene's test. The independent T-test, Mann Whitney U-test, or Kruskal Wallis test was used to analyze the quantitative data. The chi-square test or Kruskal Wallis test was to analyze the categorical variables and frequencies. Collinearity among confounding variables at different times was investigated using correlation analysis. For the primary and secondary endpoints, the 28- and 90-day, nosocomial infections, and AKI were analyzed using the chi-square test or Kruskal Wallis test, and the LOS of ICU/hospital and MV were analyzed using the independent T-test or Mann Whitney U-test. The variables considered were age, gender, body mass index (BMI), nutrition risk score 2002(NRS 2002), PNI score, acute physiology and chronic health evaluation-II (APACHE-II) score, baseline blood tests, nutrition intake (including caloric and protein intake) and time before the commencement of nutritional treatment in ICU. All analyses were performed using SPSS (version 17.0, IBM Corp., New York, USA). All tests for statistical significance were determined using an alpha level of 0.05.

3. Results

Between May 1,2019, and April 30, 2020, a total of 312 critically ill patients from 4 participating hospital ICU of the Zhejiang province in China, who accepted nutritional treatment for more than 3 days, were included. Of these, 302 patients were finally enrolled (Fig. 1). As demonstrated in Fig. 1, the following patients were excluded:2 patient who were readmitted, 5 patient who received the CRRT therapy, 1 patient who withdrew consent, 1 patient who recently admitted to another hospital and 1 patient who discontinued treatment. All patients were divided into RFS and Non-RFS groups. According to the serum phosphate level, those in the RFS group were further divided into three subgroups: Group 1 (n = 18), Group 2 (n = 60), and Group 3 (n = 30) (Fig. 1).

As shown in Table 1, the enrolled patients included medical and surgical patients, and the latter included those who underwent elective surgery or emergency surgery. Central nervous system diseases and

infectious diseases ranked as the top 2 primary diseases indicated for ICU admissions. Hypertension, type 2 diabetes, and cardiovascular disease were the top three chronic complications. There were no statistical differences in the distribution of these among the four subgroups.

Baseline characteristics are compared in Table 2. The mean age of the participants varied from 59 to 63 years of age. Women were accounted for 16.7–40%. At enrolment, the mean APACHE II score varied from 15.36 to 19.13 and this score was significantly higher in Group 2 ($p = 0.009$) and Group 3 ($p = 0.01$) than in the Non-RFS group.

Regarding the nutritional parameters, the mean time before starting EN treatment was between 33–43 hours and the percentage of those starting nutrition within 48 hours was 70%–83%. Except for the baseline NRS2002 and BMI index, no significant differences were found in the baseline data (Fig. 3 and Table 2). The NRS2002 score in Group 2 ($p < 0.001$) and Group 3 ($p = 0.001$) was higher than the Non-RFS group. Moreover, the BMI index in Group 3 was lower than the Non-RFS group ($p = 0.001$) (Table 2).

The electrolyte and glucose levels are shown in Fig. 2. There was a correlation at different times for electrolyte and serum phosphate levels. The levels were lower in Group 2 and Group 3 compared with the Non-RFS group. The serum potassium, magnesium, and calcium levels did not reach statistical significance in the different groups. The serum glucose level, 3 days after starting nutrition, was significantly different between the groups. These levels were significantly higher in Group 2 and Group 3 compared with the Non-RFS group (Fig. 2).

In terms of organ injury, Pro-BNP and total blood bilirubin were significantly increased in the RFS group after 3 days of nutrition treatment. Of those in the RFS group, Pro-BNP was highest in Group 3. The Pro-BNP level of the RFS group was higher than that in the non-RFS group. Moreover, the total bilirubin level was significantly higher in Group 2 than in Group 1 (Figure S1). There were no significant differences in other organ changes between the different groups (Figure S1, Tables 2 and 3). As depicted in Table 3, the rate of nosocomial infection in the RFS groups (Group 2 and 3) was higher than the Non-RFS group but the difference was not statistically significant.

The median time of ICU length of stay, duration of mechanical ventilation, and the 90-day mortality had no statistical significance (Table 3). The length of hospital stay in Group 2 was significantly shorter than that in the non-RFS group. Furthermore, the 28-day mortality increased. This may be associated with the short hospital LOS, and the difference was statistically significant.

According to the preliminary results, the clinical prognosis of RFS2 was worse than that of the non-RFS group. The researchers had thought that RFS2 criteria may potentially be the best diagnostic criterion. To assess this, the enrolled participants were further divided into the modified RFS group and modified non-RFS group. We found that the nutrition risk indices such as NRS2002 score and BMI index were higher in the modified RFS group than the modified non-RFS group ($p < 0.001$ and $p = 0.04$, Table S1). The APACHE II score was also higher in the modified RFS group compared with the modified non-RFS group. However,

the percent of high-risk RFS patients were not significantly different between the two modified groups (Table S1).

As shown in Table 4, the median time of ICU/hospital LOS, duration of mechanical ventilation, and the percent of AKI were not statistically significant ($p > 0.05$). The frequency of nosocomial infection was higher in the modified RFS group versus the modified non-RFS group, $p = 0.04$. Furthermore, the 28- and 90-day mortality were obviously higher in the modified RFS group, and the difference was statistically significant.

4. Discussion

The major finding of this study is that the best criterion of RFS is defined by a serum phosphate level of 0.65mmol/L and a rate of change greater than 0.16mmol/L within 72h after starting nutritional support. Patients with RFS were associated with higher disease severity, higher risk of nosocomial infections, and increased mortality at both 28 days and 90 days. The NICE standard has limitations in identifying high-risk RFS in critically ill patients by considering only a reduction in serum phosphate level to 0.32mmol/L.

Currently, the definition of RFS is highly heterogeneous and based on different electrolyte disturbances and/or clinical parameters. Hypophosphatemia after feeding is the hallmark and the RFS diagnosis relies on a cut-off and/or a relative decrease of serum phosphate level from the baseline. The range of cut-offs in defining hypophosphatemia varies from serum phosphate < 1 mmol/L to < 0.32 mmol/L and are reduction rate of $> 30\%$ from baseline, to > 0.16 mmol/L. Of note, in the study by Rio, the diagnostic criterion of RFS was defined as a serum phosphate level lower than 0.32mmol/L[5], which concurred with two other studies[7, 8]. The diagnostic criterion of below 0.65mmol/L was firstly applied in Marek's study[9], which was also cited by another study[10], and later adapted by Marvin[11]. The above criteria have been commonly used. However, the prognosis demonstrated in those studies was different from our study, and as such, we divided our RFS group into three subgroups to further assess the different diagnostic criteria of RFS. The results of this study showed that by defining RFS in terms of the RFS2 group, the BMI and NRS2002 scores in RFS patients were significantly different from that of the non-RFS patients. RFS patients had higher nutrition risk and this validated our hypothesis that patient at high nutritional risk was associated with RFS risk. Moreover, the 28-day mortality of the RFS patients significantly increased. These findings suggest that clinicians must recognize the severely at-risk patients early and intervene early. A previous study by Doig[10], using the same diagnostic criteria as our modified RFS, found that low-calorie feeding effectively improved the 60-day survival after ICU and reduced the incidence of nosocomial infections. In contrast to the results of Doig's study, Olthof [12] found that there was no difference in clinical prognosis regardless of the presence of RFS or not and concluded that low caloric intake and APACHE II score were two independent risk factors. This further validates our conclusion and supports the credibility of using the RFS2 criterion for the diagnosis of RFS. We can also infer from these results that using stringent diagnostic criteria for RFS as suggested by Rio[5] may lead to delayed treatment and deteriorated outcomes. It is feasible to identify RFS by serum phosphorus standards in critically ill patients and this provides the theoretical basis for effective guidance of hypocaloric feeding.

The identification of patients at high-risk of RFS has mainly been based on the NICE standard. However, it was not a specific evaluation index for critically ill patients. To date, there appears to be no relevant research study on the identification efficiency of critically ill patients.

In addition to validating the best diagnostic criteria, clinical studies at this stage also need to provide the theoretical basis for identifying patients at high-risk of RFS. In phase III of our research (NCT04005300), we verified the value of the NICE standard in identifying critically ill patients at high-risk of RFS. The results showed that by applying the NICE standard, the RFS3 group, but not the RFS2 group, was statistically different compared with the non-RFS group, confirming a certain predictive effect. Furthermore, this may be associated with the NICE diagnostic criteria used for the RFS3 group and partly confirmed the NICE value standard of 0.32mmol/L serum phosphate as per Rio's clinical research[5]. As mentioned, we found that the standard 0.32mmol/L serum phosphate level may lead to delays in the treatment of critically ill patients. Therefore, based on our findings, the NICE standard was not effective in guiding the identification of high-risk RFS in critically ill patients. As such, the multicenter clinical trial may be discontinued at this stage.

5. Conclusion

The serum phosphate level of 0.65mmol/L as the diagnostic criterion for RFS has obvious clinical significance and may be the best diagnostic criterion at present. The NICE standard had limitations in identifying critically ill patients at high-risk of RFS. Future phase III research should focus on new criteria for identifying high-risk RFS patients.

Declarations

Availability of data and materials: The dataset used and analyzed during the current study is available from the corresponding author on reasonable request.

Abbreviations: RFS: refeeding syndrome; LOS: length of stay; ICU: intensive care units; NRS2002: Nutrition Risk score 2002; BMI: Body Mass Index; APACHE-II: Acute Physiology and Chronic Health Evaluation-II; MV: mechanical ventilation; CRRT: continuous renal replacement therapy.

Author contributions: KL, and MH designed the study; KL, XS, XZ, XX, ZX, YX, YH, YW, JL, BY, HW, QW, HW, HZ, FS, JT, LG collect the test data; KL, XS, XC and WH analyzed the data and wrote the paper. MH, KL, WH and XC revised the article and had primary responsibility for the final content. All authors read and approved the final manuscript.

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Ethics approval and consent to participate According to the Declaration of Helsinki, this study was conducted. The clinical protocol passed ethical approval by the Ethics Committee of Second Affiliated Hospital, Zhejiang University School of Medicine (NO: I2019001223). All enrolled patients were informed consent.

Consent for publication Not applicable.

Competing interest: The authors declare that they have no competing interests. The authors declare that they have no competing interests.

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Tables

Due to technical limitations, table 1 to 4 is only available as a download in the Supplemental Files section.

Figures

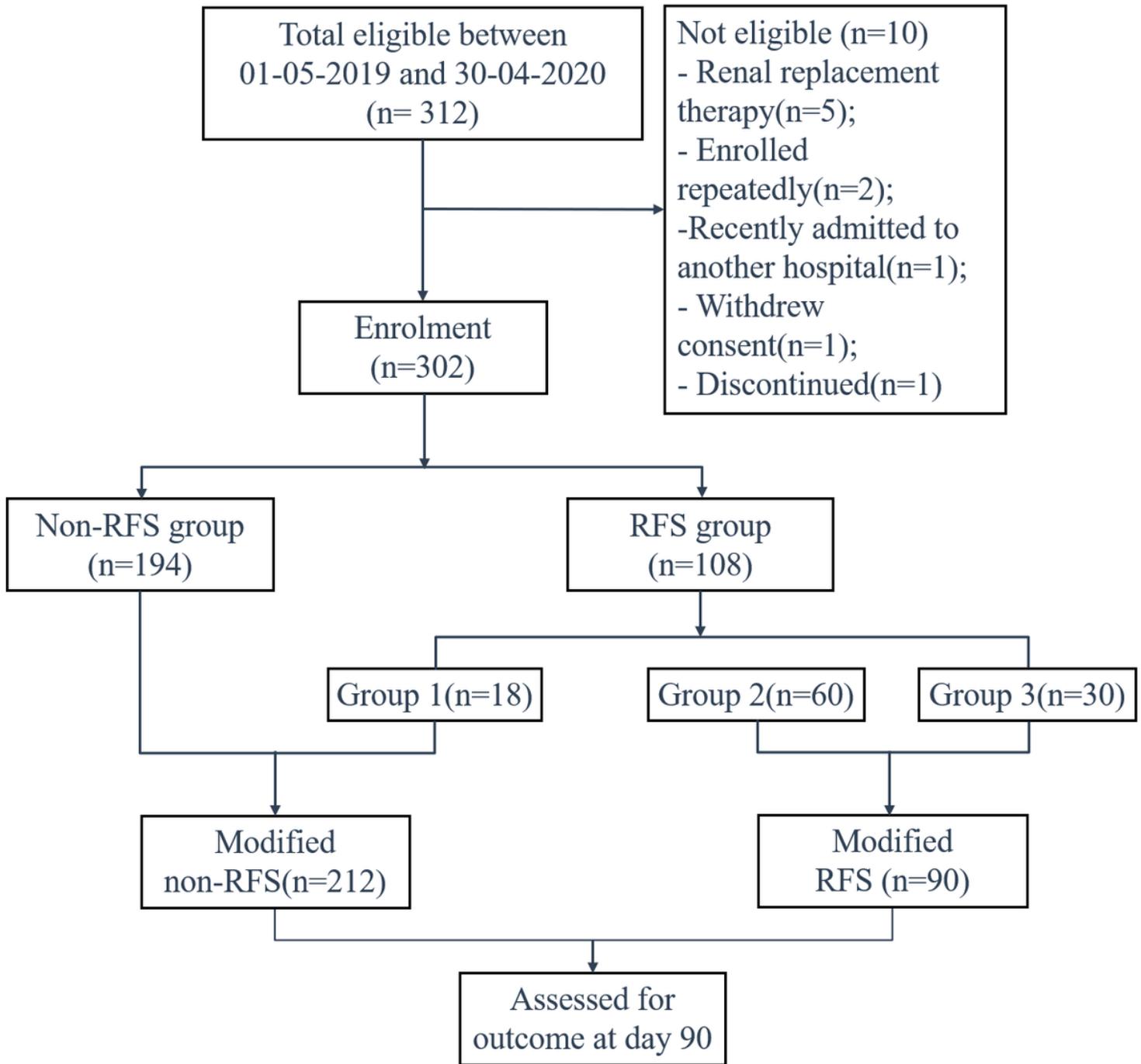


Figure 1

Flowchart of enrolled patients RFS: refeeding syndrome;

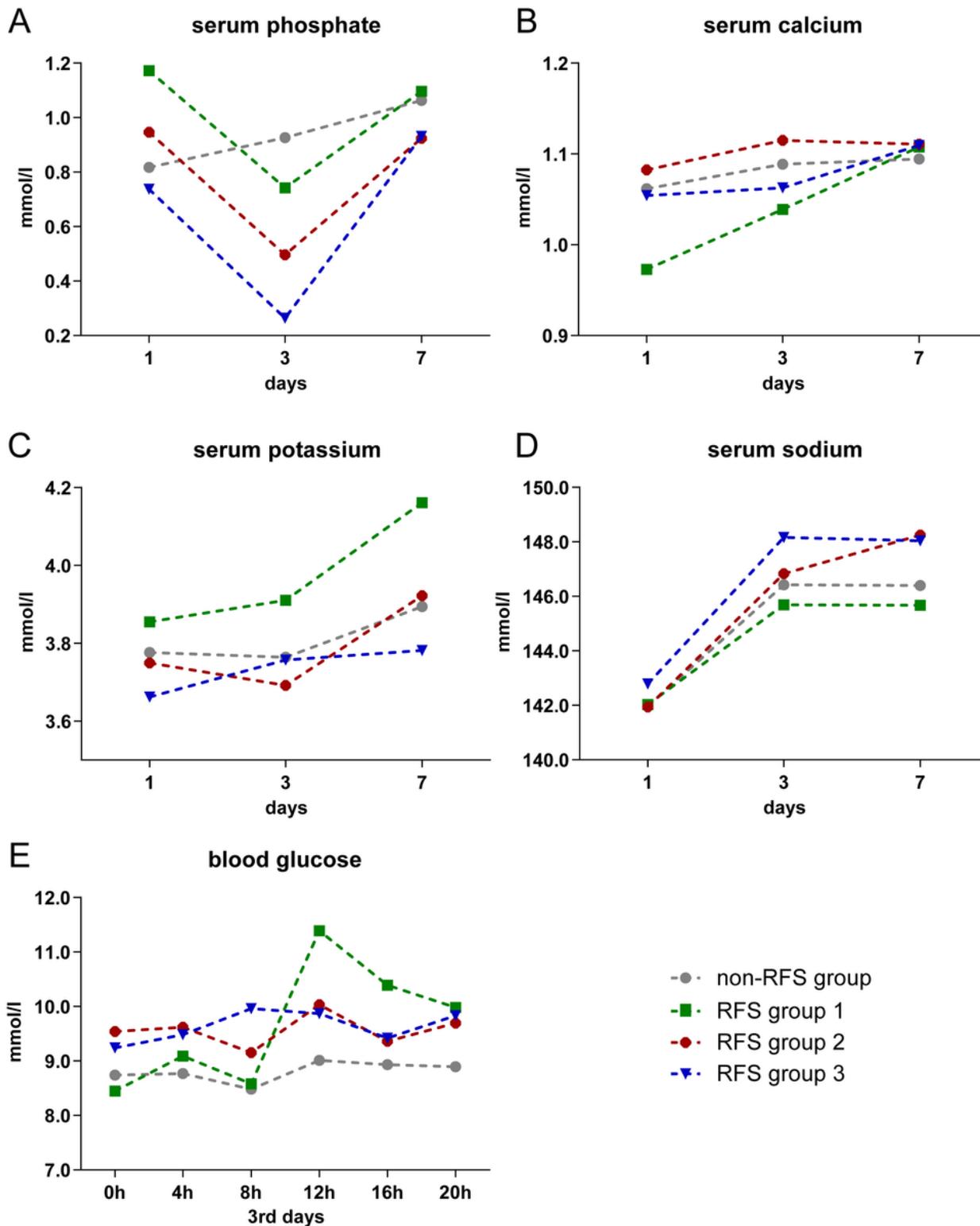


Figure 2

Course of electrolytes and glucose A. Serum phosphate changes in different groups. B. Serum Calcium changes in different groups. C. Serum potassium changes in different groups. D. Serum sodium changes in different groups. E. Blood glucose changes in different groups in third day. Measurements are depicted from the day 1, 3 and 7 of RFS diagnosis.

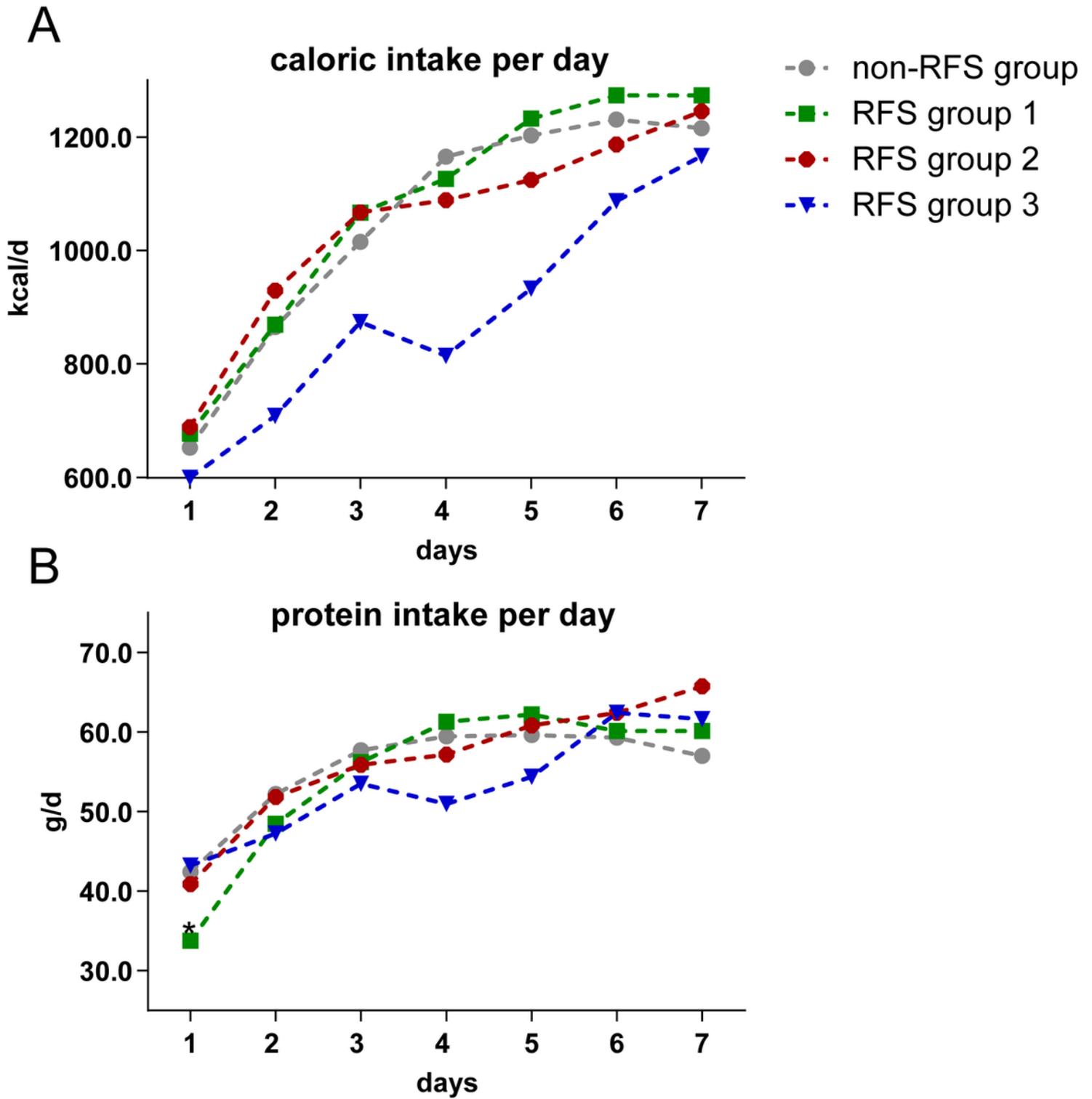


Figure 3

Calorie and protein intake A. Calorie intake in different groups. B. Protein intake in different groups.

Supplementary Files

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