Evaluation of the Refeeding Syndrome Criteria in Critically Ill Patients in a Chinese Hospital: A Retrospective Study

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Research

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Abstract

Background: Refeeding syndrome (RFS) was a group of metabolic disorders associated with refeeding after starvation. However, RFS is underdiagnosed in China due to the highly heterogeneous diagnostic criteria. This study was to evaluate the diagnosis of RFS in our intensive care unit (ICU).

Methods: Patients monitoring serum phosphate and accepting nutritional treatment more than 3 days were included in our retrospective study. RFS was defined as the new onset hypophosphatemia (<0.87mmol/l) within 72 h after feeding and serum phosphate concentration decreased more than the extent 30%. According to the lowest serum phosphate level within the first 3 days after feeding, all RFS patients were divided into the three groups: Group 1(between 0.65 and 0.87mmol/L as well as more than 30% decrease from baseline), Group 2 (between 0.32 and 0.65mmol/L as well as at least 0.16mmol/L decrease from baseline) and Group 3 (lower than 0.32mmol/L). The nutritional and prognostic indices were recorded and analyzed within the three groups.

Results: A total of 1678 patients were included, of which 150(8.7%) were regularly monitored for serum phosphate. Among these 150 patients, 27 patients were diagnosed the RFS finally. Except for NRS 2002, there were no significant difference in nutritional index such as BMI, percentage of High-risk RFS, total caloric intake, baseline of potassium, magnesium, phosphate and calcium and time to start feeding among three groups. Also, there were no significant differences in clinical outcome, duration of mechanical ventilation and LOS of ICU and hospital. The NRS2002 scores of the three groups were 0.75±0.957, 3.00±1.541 and 4.50±1.049 respectively, and the higher the decline of serum phosphate, the higher the NRS2002 score was (P=0.001).

Conclusions: The refeeding hypophosphatemia incidence was not rare in intensive care unit，even serum phosphate has not been monitored regularly. The higher score of NRS2002 might be correlated with greater decline of serum phosphate. However, changes in serum phosphate may be unrelated to prognosis and not be an optimal indicator of low calorie feeding.

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

Background

Refeeding syndrome (RFS) was a group of metabolic disorders associated with refeeding.[1] Serum hypophosphatemia was a typical clinical sign of RFS, and other metabolic disturbances, such as hypokalemia, thiamine deficiency and fluid overload, also was followed. Currently, RFS was reported as the new onset hypophosphatemia and serum phosphate concentration decreased more than the extent 30% within 72 h after feeding. However, the standard of the refeeding hypophosphatemia has not reached a consensus yet.

RFS was often found to be occurring in short-term faster patients, especially in critically ill patients. [2] Consequently, patients who were at high nutrition risk or severely malnourished should be advanced toward goal while monitoring for RFS.[3] Besides, mortality and morbidity of RFS during critical illness has not been studied well because of variable definitions, unfamiliarity of clinicians with RFS, and the complex interplay between acute illness and RFS. Some studies thought that RFS need include both clinical and electrolyte abnormalities, while in other studies, electrolyte disturbance was the only diagnostic criterion for RFS. [4, 5] [6]. The object of our study was to investigate the monitoring rate of serum phosphate and discuss the diagnostic rate of RFS in ICU.

Methods

2.1 Study population

We performed a retrospective study at the ICU of a large teaching hospital in Hangzhou of Zhejiang province. Ethical approval was granted by Institutional Review Board (NO: I2019001223) and the study protocol was registered at http://www.clinicaltrials.gov (NCT04005300).

Patients (older than 18-year-old) requiring mechanical ventilation were screened in our ICU from January 1st 2014 to April 30th 2019. All of them were accepted nutritional treatment for more than 3 days and also monitored serum phosphate. Patients were ineligible such as parathyroidectomy, receiving treatment of renal replacement therapy or phosphate binders. The readmitted subjects also were excluded. The nutritional characteristics were recorded, including age, gender, Body Mass Index (BMI), Nutrition Risk score 2002(NRS 2002), Acute Physiology and Chronic Health Evaluation-II (APACHE-II)-score, baseline blood tests and time before commencement of nutritional treatment.

Based on the different serum phosphate[7], three diagnostic criteria of RFS was set in this study for further discussion: criteria 1 (Group 1 that the serum phosphate dropped to the level between 0.65 and 0.87 mmol/L and the rate of decline was greater than 30% within 72 h after starting nutritional support), criteria 2 (Group 2 that the serum phosphate dropped to the level between 0.32 and 0.65 mmol/ L, and the change range was greater than 0.16 mmol/ L within 72 h after starting nutritional support) and criteria 3 (Group 3 that the serum phosphate concentration dropped below 0.32 mmol/L within 72 h after feeding). (Fig. 1).

2.2 Clinical analyses

Daily caloric intake of subjects, including enteral or parenteral nutrition, propofol and sodium citrate, was recorded during the first week after enrollment. The subjects of developed RFS were analyzed. According to the previous study [8], the low calorie feeding was defined as receiving less than 20 kcal/h of the starting nutritional treatment and gradually increased the calorie before target calorie at least one week.

2.3. Outcome

Primary endpoint was weight of detrimental prognosis including mortality, discharge of deteriorated and improvement. Other secondary endpoints included LOS of ICU and/or hospital, and the duration of mechanical ventilation (MV) in days.

2.4. Data collection and protection

All data were from the database in our hospital, verified by two different researchers manually, and stored on hospital computer.

2.5. Statistical analysis

Quantitative data were expressed as mean (± standard deviation (SD)), which were dichotomized or categorized if necessary, and categorical and binary variables were reported as frequency or percentage. The equality of variances was assessed by Levene's test. Independent T-test, Mann Whitney U-test or Kruskal Wallis test was to analyzed quantitative data and chi-square-tests or Kruskal Wallis test was to analyzed the categorical variables and frequencies. For the primary endpoint, the univariate effect on prognosis were included in the Kruskal Wallis test. Variables considered were: age, gender, Body Mass Index (BMI), Nutrition Risk score 2002(NRS 2002), Acute Physiology and Chronic Health Evaluation-II (APACHE-II)-score, baseline blood tests, and time before commencement of nutritional treatment. Collinearity among confounding variables at different time was investigated using correlation analysis. All analyses were performed using SPSS (version 17.0). All tests for statistical significance were determined using an alpha level of 0.05.

Results

From January 1st 2014 to April 30th 2019, 1678 patients requiring mechanical ventilation and measuring phosphate blood test accepted nutritional treatment for more than 3 days in our ICU. Total 150 cases were standard monitoring of serum phosphate, which the serum phosphate was measured daily for the first 3 days after receiving nutritional treatment. The standard detection rate of serum phosphate was about 8.7% in our study. As demonstrated in Fig. 1, 3 patients(readmitted), 6 patients (received the CRRT therapy) and 2 patients (received the phosphate binders) were excluded. 27 patients accounting for 19.4% developed RFS and were finally enrolled. Three groups were set as depicted in the method part for further discussion of the criteria of RFS, 4 cases were included in Group 1, 17 cases in Group 2 and 6 cases in Group 3(Fig. 1).

In Table 1, baseline characteristics were compared within the three groups. Except for baseline NRS 2002(Group 1 0.75 ± 0.957 vs Group 2 3.00 ± 1.541 vs 4.50 ± 1.049, $P = 0.001$), no significant differences were found in above baseline data, such as age, gender, BMI, APACHE-II, percentage of High-risk RFS, total caloric intake (kcal), baseline potassium, magnesium, phosphate, calcium, and time to start feeding.

Table 1
Patient characteristics.

	Group 1 (N = 4)	Group 2 (N = 17)	Group 3 (N = 6)	F / Z value	P value
Age(years)	50.00 ± 16.06	57.47 ± 18.06	57.50 ± 18.63	.296	.747
Gender, female	50.0%	41.2%	50.0%	.198	.906
BMI on admission	24.84 ± .78	21.73 ± 3.54	21.35 ± 2.89	.786	.478
BMI < 18.5 kg/m^2	0	2/11	0	1.349	.509
NRS 2002	.75 ± .95*	3.00 ± 1.54	4.50 ± 1.04*#	8.757	.001
APACHE II-score	7.75 ± 1.70	12.00 ± 9.11	22.50 ± 14.57	3.279	.055
High-risk RFS	0	52.9%	33.3%	5.352	.069
Percentage of time to start nutrition within 48 hours	75.0%	100%	83.3%	4.353	.113
Percentage of Enteral Nutrition	50.0%	41.2%	50.0%	.198	.906
Feeding intolerance	0	0	0		
3-day caloric intake	1562.5 ± 744.28	1791.18 ± 1041.35	1991.67 ± 1313.88	.194	.825
7-day caloric intake	3602.50 ± 3176.00	3759.41 ± 2021.38	3853.33 ± 3853.33	.014	.986
Percentage of low calorie feeding	50.0%	52.9%	50.0%	.022	.989

p Values calculated using independent sample t tests, ManneWhitney U tests, or chi-square tests where appropriate. #p < 0.05: vs group1; *p < 0.05: vs group2;

RFS: refeeding syndrome; BMI: body mass index; APACHE-II score (first 24 h of admission), acute physiology and chronic health evaluation; NRS 2002 **(first 24 h of admission)**, Nutrition risk score 2002.

Electrolyte levels were shown in Fig. 2. There was no correlation between phosphate values at different time (W = 0.990, P = 0.896), and also no difference of serum phosphate between Day 1 and Day 7 in Group 2 (p = 0.157) as well as in Group 3(p = 0.088). The time of lowest daily phosphate level was in the third day after feeding, especially in Group 3 (Fig. 2a, p < 0.001 on day 3). Furthermore, the serum of potassium, magnesium and calcium had correlation at different time, but there were not reaching statistical significance both Intra - and inter-group (Fig. 2b-d).

Among the three group, we did not find the difference in the number of the cases who were dead or against medical advice discharges because of the deterioration of disease($p = 0.17$; Table 2), although Group 3 may have a worse prognosis ($H = 23.40$, Table 2). And there was no correlation between the value of serum phosphorus reduction and prognosis ($p = 0.077$; Table 3). In addition, there was no difference between low calorie feeding and prognosis ($p = 0.151$; Table 3). Median time of ICU length of stay and duration of mechanical ventilation of group 3 was much than other two groups, but the difference had no statistical significance ($p = 0.552$ and $p = 0.776$; Table 2). The hospital LOS also had a tendency of reduction within the three groups in Table 2. ($p = 0.309$). Moreover, there was no difference in duration of mechanical ventilation within three groups ($p = 0.776$; Table 2).

Table 2
Outcome.

	Group 1 **(N = 4)**	**Group 2** **(N = 17)**	**Group 3** **(N = 6)**	**F value**	**P value**
Duration of mechanical ventilation in days	2.25 ± 2.19	5.13 ± 9.37	5.83 ± 5.93	.257	.776
ICU LOS	3.25 ± 2.06	6.53 ± 8.88	9.00 ± 9.00	.608	.552
Hospital LOS	21.25 ± 19.19	21.47 ± 7.53	13.67 ± 12.01	1.235	.309
Mortality	0/4	1/17	1/6		
Prognosis (H value)	16.50	16.64	23.40		.170

LOS: **Length of stay;**

p Values calculated using independent sample t tests, ManneWhitney U tests, chi-square tests where appropriate or Kruskal W**allis test (The higher the H value was, the worse the prognosis was); p < 0.05 = significant difference.**

Table 3
The relationship between low calorie feeding, delta phosphate and prognosis.

	Prognosis(H value)	P value
Low calorie feeding		
yes	12.55	0.151
no	9.3	
Delta phosphate(mmol/l)		
< 0.43	15.50	.077
0.43 ≤ delta < 0.7	14.25	
0.7 ≤ delta < 0.9	21.50	
0.9≤	24.64	

Discussion

The major finding of this study is that the standard monitoring of serum phosphate was only 8.7% in our ICU and the incidence of RFS was 19.4% (27/139). And the study also found that the higher the nutritional risk was, the lower the serum phosphate might be (Table 1). Some studies found that the refeeding hypophosphatemia incidence, fluctuated with 34–37% [9, 10] [11], was not rare in critically ill patients and the starvation for a period as short as 48 hours could predispose to RFS[12]. In this retrospective study, the RFS incidence was 19.4%, less than the previous study and our another prospective study(35%). During this study period, there were 4800 patients admitted in ICU, that is,the test rate of serum phosphate was about 35%(1678/4800) that may be an important reason of low RFS incidence, especially lack of standard monitoring that the recent guideline suggested monitoring electrolyte once a day for early diagnosis of RFS.[3, 13] Additionally, this retrospective analysis revealed that the patients consistent with RFS lacked relevant clinical diagnosis or treatment.

Nowadays, the definition of RFS was highly heterogeneous based on different electrolyte disturbances and/or clinical parameters. And the hypophosphatemia after feeding was the hallmark which was relying on a cut-off and/or relative decrease from baseline. The range of cut-offs in definition of hypophosphatemia varied from serum phosphate < 1 mmol/L to < 0.32 mmol/L or decreased rate from baseline > 30% to > 0.16 mmol/L. Of note, in RIO’s study, the criterion of RFS was lower than 0.32 mmol/l[5]which was identically defined in two other studies[14, 15]. The criterion that below 0.65 mmol/l was firstly applied in Marek’s study [12]which was also cited by other[8], and later slightly adapted by Marvin’s[16]. The above criteria were commonly used. However, the prognosis demonstrated in those studies was different that is the reason we set three groups to discuss the different criteria of RFS in our study.

A randomized controlled trial by Doig [8] found that low caloric intake could improve the survival rate of day 60 and increased the overall survival time in critical ill patients with RFS, although it did not increase the rate of ICU discharge. According to the results of Doig study, the researchers of Olthof [9] found that there was no differences in clinical prognosis whether RFS or not, but low caloric intake could decreased the 6-month mortality risk in RFS patients that non-RFS patients did not. However, in our retrospective study, low caloric intake did not improve the clinical prognosis in RFS patients. Some study[4, 5] which used the RFS definition of serum phosphate concentration decreased to below 0.32 mmol/L within 72 h after feeding, found that death was rarely accompanied by RFS. And RFS could not be prevented by identification of risk and treatment with hypocaloric feeding. Similarly, they could not find relationship between prognosis and low caloric intake.

In this study, there was no significant difference in outcome, including ICU and hospital LOS, duration of mechanical ventilation and mortality in three criteria of RFS. And there was no significant difference in clinical outcomes between whether low caloric intake or not. Also, no differences between the change value of decline in serum phosphate and prognosis. However, the study found that, although there was no statistical difference, serum phosphorus level might be correlated with disease severity.

Because of lacking of non-specifically clinical characteristics, RFS was simply defined by hypophosphatemia. However, as to the retrospective study, it lacks of uniformly low caloric intake applied, and lead to confounding and selection bias that cannot be avoided.

Conclusions

The refeeding hypophosphatemia incidence was actually not rare in ICU,even serum phosphate has not been monitored regularly. The score of NRS2002 might be positively correlated with the decline level of serum phosphate. Due to the limitation of sample sizes, there was no significant difference in results. So, we could not draw a clear conclusion which criteria of RFS was the best indication to receiving the low caloric feeding. Future efforts to increase the sample size and our nutritional group will be launching a multicenter, clinical randomized controlled trial to further prove the best serum phosphate intervention criteria for RFS.

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.

Declarations

Availability of data and materials

The dataset used and analyzed during the current study is available from the corresponding author on reasonable request.

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). Due to the retrospective nature of the study, informed consent was waived.

Consent for publication Not applicable.

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

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Author contributions: Lu Kongmiao, and Huang Man designed the study; Lu Kongmiao, Zheng Xiangxin, Wan Huqiang and Wang Qianwen collect the test data; Lu Kongmiao and Chen Xiaomeng analyzed the data and wrote the paper. Han Wei and Chen Xiaomeng revised the article and had primary responsibility for the final content. All authors read and approved the final manuscript.

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Figures

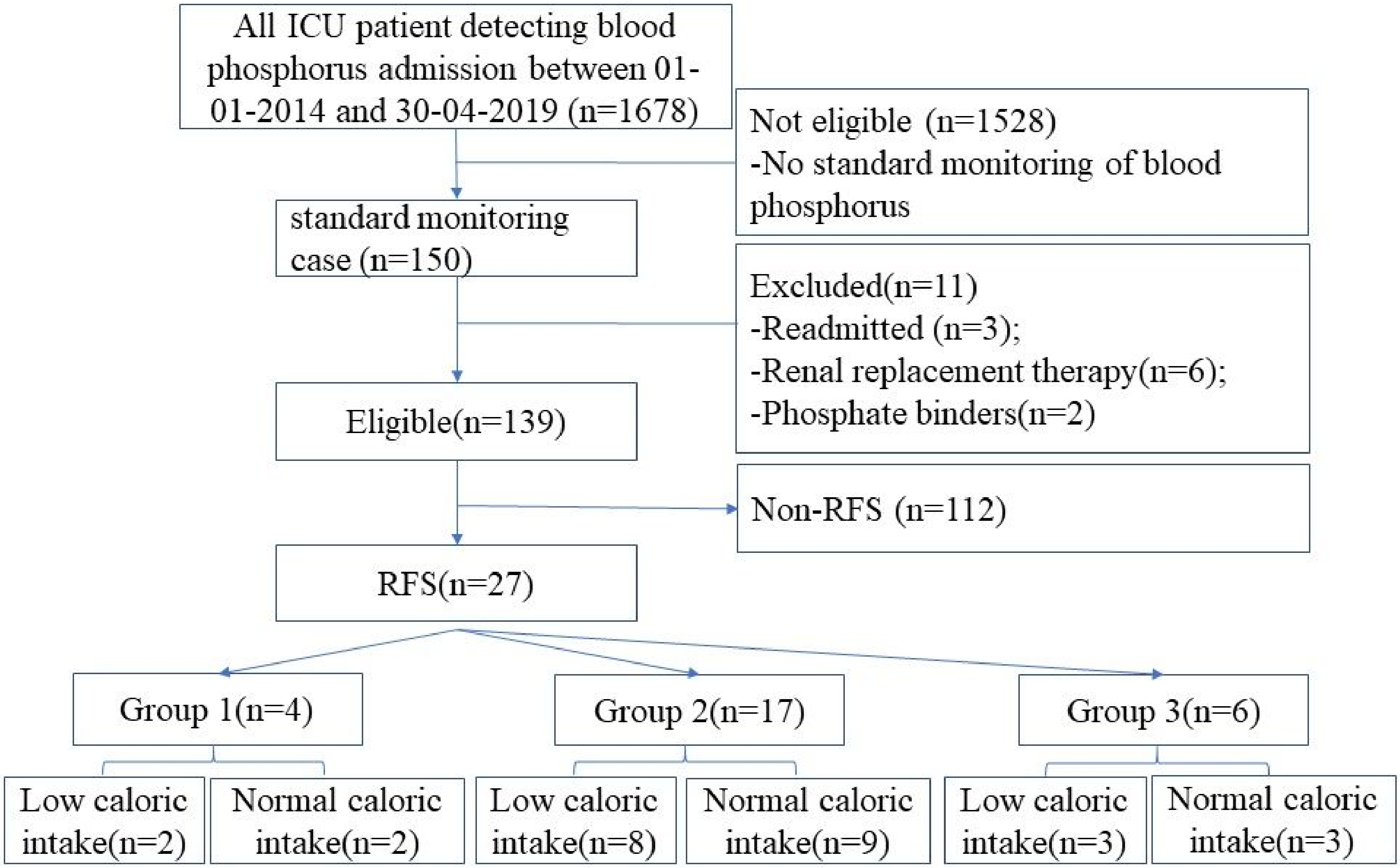

Figure 1

Flowchart of enrolled patients RFS：refeeding syndrome;

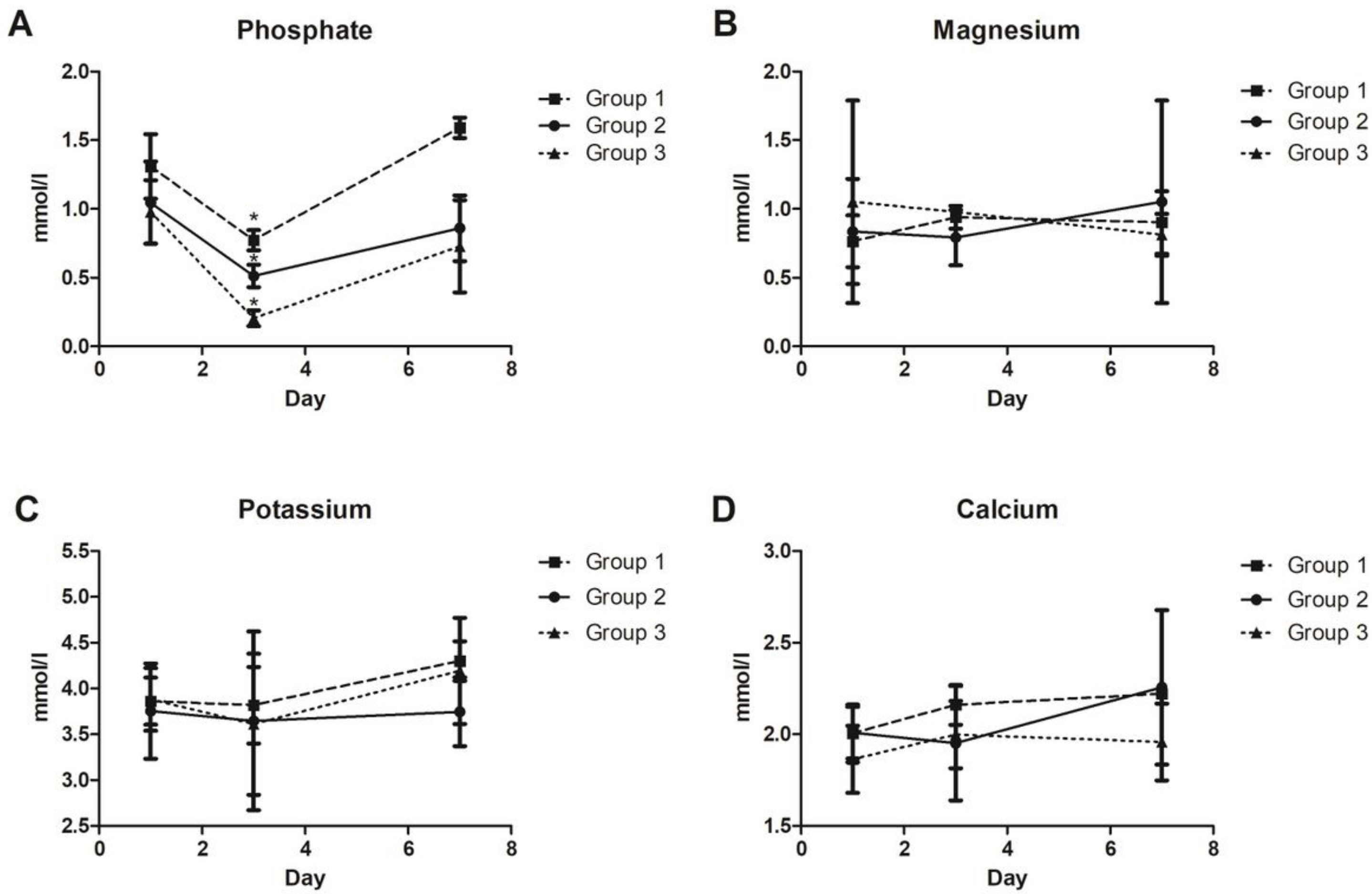

Figure 2

Course of electrolytes. p Values calculated using independent sample chi-square tests, or ManneWhitney U tests where appropriate. * $p < 0.05$: vs day 1; Error bars indicate 95% CI for mean differences between the groups. Measurements are depicted from the day 1, 3 and 7 of RFS diagnosis. a) Serum phosphate changes in different groups. b) Serum magnesium changes in different groups. c) Serum potassium changes in different groups. d) Serum calcium changes in different groups