Original Article

Refeeding hypophosphataemia after enteral nutrition in a Malaysian intensive care unit: risk factors and outcome

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Background and Objectives: Refeeding hypophosphataemia (RH) is characterized by an acute electrolyte derangement following nutrition therapy. Complications associated include heart failure, respiratory failure, paraesthesia, seizure and death. We aim to assess its incidence, risk factors, and outcome in our local intensive care unit (ICU). **Methods and Study Design:** A prospective observational cohort study was conducted at the mixed medical-surgical of a tertiary ICU in Kuantan, Malaysia. The study was registered under the National Medical Research Register (NMRR-14-803-19813) and has received ethical approval. Inclusion criteria include adult admission longer than 48 hours who were started on enteral feeding. Chronic renal failure patients and those receiving dialysis were excluded. RH was defined as plasma phosphate less than 0.65 mmol/L and a drop of more than 0.16 mmol/L following feeding. **Results:** A total of 109 patients were recruited, of which 44 (42.6%) had RH. Patients with RH had higher SOFA score compared to those without (p=0.04). There were no differences in the APACHE II and NUTRIC scores. Serum albumin was lower in those with RH (p=0.04). After refeeding, patients with RH had lower serum phosphate, magnesium and albumin, and higher supplementation of phosphate, potassium and calcium. There were no differences in mortality, length of hospital or ICU stay. **Conclusions:** Refeeding hypophosphataemia occurs in almost half of ICU admission. Risk factors for refeeding include high organ failure score and low albumin. Refeeding was associated with imbalances in phosphate, magnesium, potassium and calcium. Future larger study may further investigate these risk factors and long-term outcomes.

Key Words: refeeding syndrome, refeeding hypophosphataemia, organ failure, intensive care unit, risk factors

INTRODUCTION

Refeeding syndrome refers to serious metabolic and biochemical disturbances that can occur in starved and/or malnourished patients on recommencement of feeding.[1] However, it has been described in patients starved for as short as 48 hours.[2] It is characterized by acute metabolic and electrolyte derangements including hypophosphataemia, hypomagnesaemia, hypokalaemia, hypocalcaemia, vitamin deficiencies (especially thiamin) and glucose intolerance.[3] Hypophosphataemia is the hallmark biochemical disturbance in refeeding syndrome, which leads to the refeeding hypophosphataemia (RH) term.[2,4] During refeeding, insulin secretion and shift of glucose metabolism increase demand for the production of phophorylated intermediates to form ATP and 2,3-DPG, which results in reduction of serum phosphate concentration.[5] Consequences of severe hypophosphataemia include arrhythmias, seizures, cardiac failure, respiratory failure, rhabdomyolysis, coma and sudden death.[5]

Several risk factors related to the physiology of starvation were associated with RH,[6,7] which include chronic malnutrition,[8,9] chronic alcoholism,[10] prolonged fasting, anorexia nervosa,[10] low serum prealbumin,[2] low baseline serum magnesium,[11] and oncology and postoperative patients.[1] Assessment of nutritional risk in critically ill patients is important to strategize the nutritional protocol to avoid RH or/and undernutrition.[1] Heyland et al[12] described the nutrition in critically ill patients' score (NUTRIC score) for risk stratification of patients at risk of malnourishment. Recently, modified NUTRIC score (without interleukin-6) has been validated as nutrition risk assessment tool in critically ill patients in Asian population and shown to be independently associated with 28-day mortality.[13] To the best of our knowledge, there are limited data on the incidence of RH in critically ill patients in Asian population. In this study, we assessed the incidence and outcome of RH in a prospective observational study in a Malaysian Intensive Care Unit (ICU). In addition, we evaluated the risk factors associated with the development of RH.

METHODS

This prospective observational study was conducted in a single center of a tertiary ICU in Hospital Tengku Ampuan Afzan Kuantan, Malaysia. The study was registered

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with the National Medical Research Register (NMRR-14-803-19813). Ethical approval was obtained from the Medical Ethics and Research Committee (MREC Number P14-909) and the International Islamic University Ethics Committee (IREC Number 277). As only routinely available clinical information was collected, the need for informed consent was waived. The inclusion criteria for this study were patients older than 18 years old and duration of ICU stay of at least 48 hours. All patients admitted to the ICU who received enteral feeding within the study period from June 2015 to May 2016 were considered for inclusion screening. Patients with diabetic ketoacidosis, and end stage renal failure on dialysis were excluded from the study. In this study, RH was considered in patients with drop of serum phosphate to less than 0.65 mmol/L with a drop of more than 0.16 within 7 days of ICU admission.[2] Patients with severe hypophosphataemia of less than 0.32 mmol/L on ICU admission and those who received enteral feed less than 48 hours were excluded from the study.

Patient's clinical records and ICU charts were reviewed for baseline and daily serum albumin, phosphate, magnesium, potassium and calcium concentrations. Demographic profiles including age, gender, race, height, weight, admission diagnosis, past medical history, length of ICU and hospital stay, duration of mechanical ventilation, concurrent medications, electrolyte supplementations and death status were extracted from the ICU charts and clinical records. Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) were used to assess severity of illness in each patient. Risk factors were defined for each patient based on the modified NUTRIC score[12] that involve age, APACHE II, SOFA, comorbidities, days from hospital to ICU admission and without interleukin-6 concentration. Other risk factors such as body mass index (BMI), mid upper arm circumference (MUAC), baseline concentrations of albumin, phosphate, magnesium, or potassium prior to refeeding were also included in this study.

Plasma phosphate, magnesium, calcium, potassium and albumin were analyzed using the Olympus AU2700TM chemistry-immunoanalyser (Olympus, Philadelphia, USA). Serum calcium concentration was corrected for hypoalbuminaemia. Mid upper arm circumference (MUAC) was measured in all patients by taking the circumference of the arm between tip of shoulder and tip of bent elbow. Actual body weight was recorded from estimation by the research personnel on the most recent weight recorded prior to ICU admission. Ideal body weight (IBW) was calculated using formula of 50 + 0.91 [height (cm) – 152.4] kg in males, and 45.5 + 0.91 [height (cm) – 152.4] kg in females.14 IBW was used to determine energy goal with the feed goal of 25-30 kcal/kg/day. If BMI was less than 18, actual body weight was used. In obese patients with BMI of more than 30, the energy goal was reduced to 22-25 kcal/kg IBW/day.[15]

Statistical analysis

Statistical analyses were performed using PASW® version 18.0 (IBM, Somers, New York, USA). Results were presented as mean ± standard deviation (SD) for normally distributed variables (parametric) or median (interquartile range or IQR) for non-normally distributed variables (non-parametric). For continuous variables, differences in two variables were analyzed using independent-t test for parametric data, or Mann-Whitney U test for non-parametric data. For categorical variables, differences in proportions were analyzed using Chi-Square test.

RESULTS

Study inclusion

One hundred and seventeen patients were initially recruited into the study. Of this, two patients with severe hypophosphataemia of less than 0.32 mmol/L on ICU admission were excluded from the analysis. Another six patients who received enteral feeding of less than 48 hours were excluded from the study (Figure 1). Of this, 44 (40.4%) had RH, defined as plasma phosphate of less than 0.65 mmol/L and a drop of more than 0.16 mmol/L after institution of enteral feeding. Five patients (4.6%) had severe hypophosphataemia of less 0.32 mmol/L.

Demographic, clinical profiles and outcomes

There were no differences in the demographic profiles or clinical characteristics between patients with and without RH (Table 1). Two patients had BMI of less than 18; both did not have RH. There were four oncology patients, of whom only one had RH. There were no differences in actual or ideal body weight between patients with and without RH. (p=0.90 and 0.74, respectively)

NUTRIC scores and clinical outcomes

Phosphate concentration reached minimum at a mean of 3.39±1.44 days, with no difference in patients with and without RH (Table 2). Patients with RH had higher SOFA score compared to those without RH (p=0.02; Figure 2). There were no differences in the APACHE II, NUTRIC score or in high nutrition risk category (NUTRIC >4) between patients with and without RH. Serum albumin was lower in patients with RH (p =0.04). Thirty-one patients (26.3%) died, with no differences in mortality, and

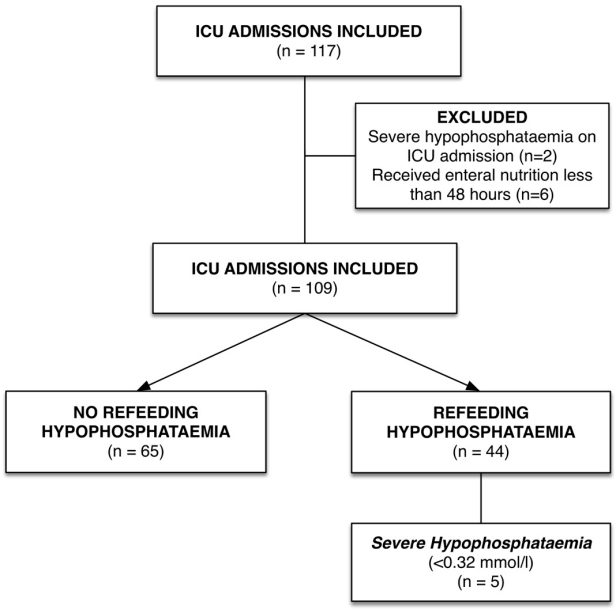

Figure 1. Patients' flow chart.

Table 1. Demographic, clinical profiles and outcome

Variables	All patients (n=109)	Refeeding hypophosphataemia (n=44)	No refeeding hypophosphataemia (n=65)	*p*
Age	51±16	52±18	50±17	0.56
Ethnicity				0.08
Malay	84 (77.1)	33 (75.0)	51 (78.5)	
Chinese	14 (12.8)	6 (13.6)	8 (12.3)	
Indian	5 (4.6)	1 (2.3)	4 (6.2)	
Orang Asli	4 (3.7)	4 (9.1)	0 (0)	
Foreigner	2 (1.8)	0 (0)	2 (3.1)	
Sex (Male)	68 (62.4)	28 (63.6)	40 (61.5)	0.84
Weight	70±16	70±18	70±15	0.92
Height	160±9	159±9	161±9	0.26
Body mass index (BMI)	27.2±7.0	27.8±8.6	26.8±5.6	0.48
Ideal body weight (kg)	58±8	56±8	59±8	0.74
Mid upper arm circumference (MUAC) (cm)	28±4	28±5	28±4	0.70
Risk based on MUAC				0.86
Low risk	14 (12.8)	6 (13.6)	8 (12.3)	
Moderate risk	75 (68.8)	31 (70.5)	44 (67.7)	
High risk	20 (18.3)	7 (15.9)	13 (20.0)	
Diagnostic class				0.21
Surgical	58 (53.2)	26 (59.1)	32 (49.2)	
Medical	51 (46.8)	18 (40.9)	33 (50.8)	

Data expressed as mean±SD, n (%), or median (lower quartile–upper quartile). Comparison of variables between the two groups was analysed using the independent t test for normally distributed variables or the Mann-Whitney test for non-normally distributed variables. Categorical variables were compared with chi-square test.

Table 2. NUTRIC scores and clinical outcomes

Variables	All patients (n=109)	Refeeding hypophosphataemia (n=44)	No refeeding hypophosphataemia (n=65)	*p*
Day of minimum PO_4^{2-} after refeeding	3.42±1.46	3.23±1.23	3.55±1.57	0.25
NUTRIC score	2.8±1.8	3.1±1.7	2.6±1.8	0.14
Age points	0.64±0.60	0.64±0.53	0.65± 0.65	0.93
Co-morbidity points	0.23±0.42	0.25±0.44	0.22±0.41	0.68
SOFA points	0.75±0.76	0.95±0.75	0.65±0.76	0.04
APACHE II points	0.78±0.84	0.91±0.91	0.69±0.79	0.19
Days from hospital to ICU admission points	0.40±0.49	0.36±0.49	0.43±0.50	0.59
NUTRIC score >4	35 (32.1)	16 (36.4)	19 (29.2)	0.43
APACHE II score	15.6±6.0	16.8±6.4	14.9±5.6	0.09
SOFA score	6.4±3.3	7.2±3.1	5.9±3.4	0.04
Albumin (g/l)	24.7±5.5	23.6±5.7	25.5±5.3	0.04
Inotropic/vasoconstrictor	55 (50.5)	27 (61.4)	28 (43.1)	0.06
Mortality	23 (21.1)	11 (25.0)	12 (18.5)	0.41
Duration of mechanical ventilation (days)	10.2±9.5	10.7±11.6	9.8±7.9	0.65
Length of ICU stay (days)	12.0±8.8	11.7±10.6	12.2±7.5	0.83
Length of hospital stay (days)	23.2±15.4	21.6±17.7	24.3±13.6	0.45

NUTRIC Score: Nutrition in the ICU score; APACHE II score: Acute Physiological and Chronic Health Evaluation II score; SOFA score: Sequential Organ Failure Score.
Data expressed as mean±SD, n (%), or median (lower quartile–upper quartile). Comparison of variables between the two groups was analysed using the independent t test for normally distributed variables or the Mann-Whitney test for non-normally distributed variables. Categorical variables were compared with chi-square test.

three of five patients (60%) with severe hypophosphataemia died. There were also no differences in length of ICU or hospital stay, or duration of mechanical ventilation.

Serum electrolytes & supplementations

The baseline phosphate concentration on ICU admission was 1.12 ±0.47, lower in patients with RH compared to those without RH (p=0.01; Table 3). Serum phosphate concentration reduced after feeding in both groups of patients, more so in those with RH (0.51±0.12). A median of 20 (10 to 40) mmol of phosphate supplementation was given to all patients, higher in those with RH compared to those without RH (p<0.0001). Serum magnesium concentration was similar at baseline in both groups. After refeeding, serum magnesium was lower in those with RH compared to the group without RH (p=0.04). Two patients had hypomagnesaemia of less than 0.5; both had RH. There were no differences in magnesium supplementation given in both groups of patients. There were no

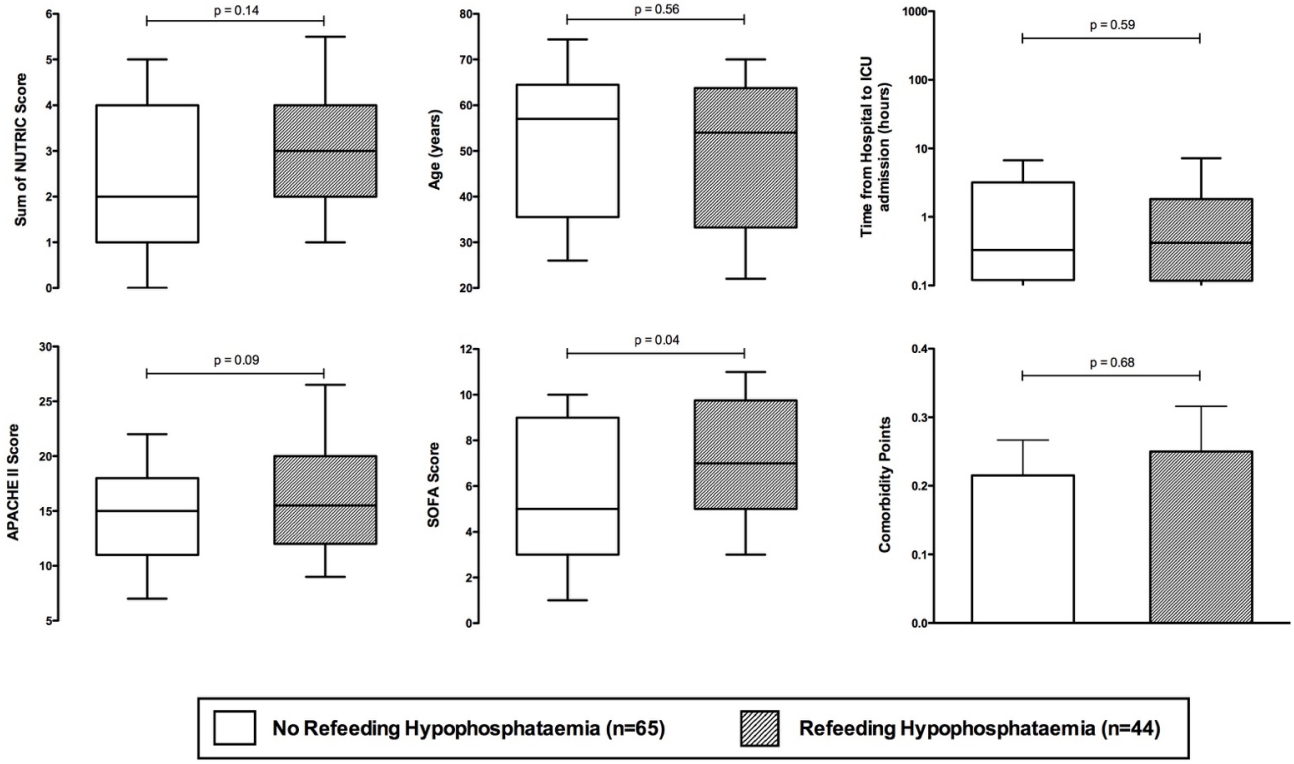

Figure 2. Box-plot of NUTRIC score and its components between patients with and without refeeding hypophosphataemia. Shown are the median, interquartile range and 10-90th percentile in each category. Comparisons were analysed using Mann Whitney U test

Table 3. Serum electrolytes and supplementations

Variables	All patients (n=109)	Refeeding hypophosphataemia (n=44)	No refeeding hypophosphataemia (n=65)	*p*
Serum phosphate (mmol/L)				
ICU admission	1.20±0.43	1.16±0.44	1.23±0.43	0.39
After feeding started	0.72±0.24	0.51±0.12	0.86±0.19	<0.0001
Suplementation (mmol)	20 (10–40)	30 (20–50)	20 (0–30)	<0.0001
Serum magnesium (mmol/L)				
ICU admission	0.78±0.23	0.77±0.28	0.80±0.19	0.45
After feeding started	0.84±0.12	0.82±0.11	0.86±0.13	0.04
Suplementation (mmol)	30 (20–50)	35 (20–50)	30 (12–40)	0.17
Serum potassium (mmol/L)				
ICU admission	3.95±0.59	3.93±0.60	3.96±0.59	0.73
After feeding started	3.45±0.43	3.38±0.46	3.50±0.40	0.16
Suplementation (g)	1 (0–3)	1 (0–5)	0.5 (0–2.0)	0.02
Serum calcium (mmol/L)				
ICU admission	2.17±0.21	2.13±0.22	2.20±0.20	0.09
After feeding started	2.10±0.27	2.10±0.24	2.11±0.30	0.92
Suplementation (mmol)	0 (0–10)	0 (0–10)	0 (0–7.5)	0.33

Data expressed as mean±SD, n (%), or median (lower quartile–upper quartile). Comparison of variables between the two groups was analysed using the independent t test for normally distributed variables or the Mann-Whitney test for non-normally distributed variables. Categorical variables were compared with chi-square test.

differences in serum potassium on ICU admission and after refeeding in both groups. However, higher potassium supplementations were needed in patients with RH (p=0.007). Baseline calcium concentration was lower in patients with RH compared to the patients without RH. However, there were no differences in calcium concentrations after refeeding nor in calcium supplementations. Albumin concentration was lower in patients with RH compared to the patients without RH (p=0.04).

Feeding

Feeding was started at a median time of 9.0 (4.4–15.9) hours after ICU admission (Table 4). The time required to achieve full energy requirement in these patients was 32 (27–42) hours. There were no differences in the time to start feeding, and the time required to achieve full energy requirement between patients with and without RH. Energy adequacy on day 1 was 64 (42–86)%, reaching to 96% on day 2 and 99% on day 3. There were no differences in energy adequacy between patients with and

Table 4. Enteral supplementation data

		All patients (n=109)	Refeeding hypophosphataemia (n=44)	No refeeding hypophosphataemia (n=65)	*p*
Time of starting nutrition after ICU admission (hours)		9.0 (4.4–15.9)	8.1 (4.4–14.9)	9.5 (4.6–19.5)	0.54
Nutritional goal (25 kcal/kg)		1449±191	1417±199	1471±185	0.14
Calories administered and adequacy					
Time to reach full calories after started feeding (hours)		32 (27–42)	32 (27–40)	33 (27–42)	0.71
Day 1	Total (kcal)	970 (586–1210)	930 (575–1270)	972 (601–1190)	0.81
	Adequacy (%)	64 (42–86)	66 (37–87)	62 (42–84)	0.97
Day 2	Total (kcal)	1517 (850–1633)	1510 (1300–1682)	1445 (928–1631)	0.23
	Adequacy (%)	96 (70–113)	104 (82–120)	92 (65–110)	0.09
Day 3	Total (kcal)	1420 (942–1640)	1520 (827–1643)	1440 (1110–1620)	0.60
	Adequacy (%)	99 (72–113)	108 (57–118)	95 (72–110)	0.13
Day 4	Total (kcal)	1340 (910–1630)	1400 (896–1661)	1350 (1110–1620)	0.70
	Adequacy (%)	100 (68–113)	102 (57–114)	97 (77–110)	0.68
Day 5	Total (kcal)	1280 (415–1625)	1332 (582–1653)	1350 (1062–1617)	0.53
	Adequacy (%)	93 (62–108)	93 (36–113)	93 (65–106)	0.97

Data expressed as mean±SD, or median (lower quartile–upper quartile). Comparison of variables between the two groups was analysed using the independent t test for normally distributed variables or the Mann-Whitney test for non-normally distributed variables.

without RH. No differences were also noted when actual body weight is used to determine the feeding goal.

DISCUSSION

In this prospective observational study, we showed that RH occurs in about 40% of ICU admission, while 4% of them had severe hypophosphataemia. Patients with RH had higher organ failure score, and lower serum albumin concentrations. After refeeding, patients with RH had lower serum phosphate and magnesium concentrations and higher supplementations of phosphate, potassium and calcium. There were no differences in the NUTRIC score or in short-term outcomes.

Hypophosphataemia is common in the intensive care setting.[16] In 208 surgical ICU patients, hypophosphataemia of less than 0.80 mmol/L was reported in 29% of their patients.[17] Hoffman et al reported 45% of 621 patients who developed hypophosphataemia of less than 0.5 mmol/L in a large academic hospital, occurred in an intensive care setting.[16] In a previous study done in our ICU, 29% of 41 patients were reported to have hypophosphataemia of less than 0.8 mmol/L.[18] In another study in our local ICU, 45% of the 29 patients had hypophosphataemia of less than 0.65 mmol/L.[19] In this larger study, we reported 40% of 109 recruited patients had refeeding hypohosphataemia after institution of enteral feeding. Of more than 10 thousand hospitalized patients, 0.43% had severe hypophosphataemia of less than 0.32 mmol/L which was associated with 4-fold increase in mortality.[8] Five (4.6%) of our patients had severe hypophosphataemia, almost similar to other studies by Marik and Bedigan[2] (9.8%) and Coskun et al[20] (5.1%). Severe hypophosphataemia is associated with very high mortality and could be life threatening if not corrected.[21,22]

Refeeding syndrome is a broader term of acute metabolic and electrolyte derangements including hypophosphataemia, hypomagnesaemia, hypokalaemia, hypocalcaemia, vitamin deficiencies (especially thiamin) and glucose intolerance.[3] The hallmark sign of refeeding syndrome is serum hypophosphataemia, leading to the term of RH.[2,3] Phosphate is essential for various physiological function of the body.[23] In patients with RH, the extreme metabolic disturbance could result in an array of organ dysfunction including the cardiovascular, respiratory, or neurological.[23,24] A simple and objective process to identify patients with refeeding syndrome can be achieved by screening for the hallmark clinical sign of hypophosphataemia associated with the initiation of nutritional therapy followed by exclusion of patients with hypophosphataemia attributable to other major causes such as ongoing dialysis, recent parathyroidectomy or treatment of hypophosphataemia.[3] Utilizing a broader definition of refeeding syndrome by O'Connor et al,[5] 93 (78.8%) of our participants had either serum phosphate of <0.7 mmol/L, potassium of <3.5 mmol/L, or magnesium of <0.5 mmol/L, and 79 (66.9%) had cardiovascular and respiratory organ failure on ICU admission.[11] Hence in this study, we chose the definition used by Marik[2] and Doig,[3] as a broader definition by O'Connor et al[5] and Rio et al[11] comprises of a larger proportion of our population due to higher severity of illness with preexisting organ failure prior to ICU admission.

The data on incidence of RH in critically ill patients are very limited especially among Asian population. Furthermore, the incidence varies with different definition of RH. In this study, we utilized the definition based on serum phosphate concentration from a study by Marik and Bedigian.[2] Based on this definition, they reported RH incidence of 34% in a mixed medical and surgical ICU.[2] In a recent multi-center randomized single-blind controlled trial, the same definition was used.[3] In a retrospective study of 117 medical ICU patients, RH was found in 52.1% after enteral and parenteral nutrition by using a definition of serum phosphate of less than 0.77 mmol/L.[20] The higher incidence of RH in this study[20] as compared to Marik and our study may be explained by higher APACHE II score in their cohort. Furthermore, they used slightly higher serum phosphate concentration as the definition of RH.

Several risk factors related to physiology of starvation had been associated with the development of RH. We showed that risk factors for RH include high organ failure

score, low albumin, and low baseline serum phosphate and calcium. Low baseline serum magnesium was shown to be an independent predictor of this syndrome.[11] Assessment of nutritional risk of critically ill patients is important in strategizing the nutritional protocol to avoid RH or/and under-nutrition. Several guidelines have been used to assess malnutrition including the Malnutrition Universal Screening Tool,[25] Nutritional Risk Screening 2002,[26] and Chinese Medical Association.[27] However, most scores consider all critically ill patients are at a high risk in their scoring or risk assessment due to the presence of acute illness.

In 2011, Heyland et al[12] developed NUTRIC score to quantify nutrition risk in ICU patients. This score involves age, APACHE II, SOFA, number of comorbidities, days from hospital to ICU admission and IL-6 concentration, which were obtained from multivariable logistic regression model involving 597 ICU patients. Higher score is associated with increased mortality and duration of mechanical ventilation, which could discriminate 'nutritional risk' in the critical care setting as other scoring system considered all ICU patients as high risk. However, in our study, we showed no difference in the overall modified NUTRIC score between patients with and without RH. We also found that there was no difference between high risk group (NUTRIC score ≥5) and low risk group with regards to RH. Of all the components of the NUTRIC score, only SOFA score was higher in patients with RH.

We also analyzed its association with outcome including mortality, length of hospital and ICU stay, and duration of mechanical ventilation. We found that none of them were associated with RH. We postulate that this is because of high severity of illness in our patients' group that mask the effect of RH in our samples. The small sample size in our cohort further impede any chance of seeing the differences. The study was not powered to see such differences. In addition, this study is an observational study, and hence we did not compare between restricted energy intake and standard protocol. We suggest a larger multicenter trial powered to look at the differences in morbidity and mortality, and that compare between restricted energy intake and standard protocol would be of value in the future. Zeki et al reported there was no increased mortality rate in the first 7 days of ICU stay in patients who developed RH following enteral and parenteral feeding.[7] Several studies showed the association of hypophosphataemia with mortality.[17,22] However, when adjusted for other risk factors, hypophosphataemia was not independently associated with ICU or hospital mortality in 2730 critically ill patients,[28] or in 321 acute kidney injury patients on dialysis.[29] RH was associated with longer hospital stay,[2,28,30] and duration of mechanical ventilation.[2,20,28]

Patients were started on feeding at a median of 9 hours after ICU admission, and full feeding was achieved at about 40 hours later. This was almost similar to another study conducted in a Malaysian setting which showed feeding was started at a median of 15 hours, and achievement of full feeding in about 1.8 days.[31] However, we showed that RH was not associated with the duration of starting nutrition after ICU admission, time required to achieve full energy requirement or amount of energy delivered.

Study limitations and future studies

This study has several limitations; first, it was conducted in a single center, and involved only a small sample size. Despite this, we showed a high incidence of RH in our population, hence suggesting careful attention should be considered in monitoring the electrolytes concentrations after feeding has been started, and any abnormal values should be corrected.[32] Thiamin replacement might be of value in those at high risk of malnutrition.[33] Second, we did not measure thiamin or trace elements or biomarkers for malnutrition e.g. interleukin-6. Further studies to investigate this would be of value. Thirdly, we did not assess the duration of fasting as we have shown before that this information is difficult to obtain from relatives since the patients are mostly unconscious during admission. In addition, we have shown previously that duration of fasting was not associated with RH.[19] Fourthly, the independent risk factors for development of RH in our local population could further be investigated in a larger group of patients. In addition, the association of RH with long-term outcomes could be further explored. Finally, we used simplistic weight-based equation as 25 kcal/kg/day to determine energy goal. Ideally, energy requirement should be determined by indirect calorimetry.

Conclusion

Refeeding hypophosphataemia is common, occurring in almost half of ICU admission who were fed enterally. Risk factors for refeeding include high organ failure score and low serum albumin. Refeeding was associated with imbalances in phosphates, magnesium, potassium and calcium. Careful attention on electrolytes concentrations post enteral or parenteral feeding is important to reduce complications associated with RH. Future larger studies may further investigate these risk factors and its association with long-term outcomes.

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AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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