Occurrence and predictors of refeeding syndrome in adult patients receiving parenteral nutrition at a Malaysian teaching hospital: A retrospective study

doi: 10.6133/apjcn.202503/PP.0011
Published online: March 2025

Running title: Predictors of refeeding syndrome in PN patients

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ABSTRACT

Background and Objectives: Refeeding syndrome (RS) is a potentially life-threatening condition characterised by significant electrolyte and fluid imbalances, posing a considerable risk in patients undergoing parenteral nutrition (PN) therapy. This study aimed to determine the occurrence, risk factors, severity, and complications of RS in a teaching hospital in Malaysia. **Methods and Study Design:** A retrospective observational study was conducted using universal sampling from October to December 2023. Data were collected for adult patients receiving PN for more than 48 hours between July 2022 and July 2023 at Hospital Canselor Tuanku Muhriz. **Results:** Among 90 patients included, 30 (33.3%) developed RS. Upon consideration of interaction terms due to collinerity of variables, a statistically significant correlation was observed between pre-existing electrolyte derangements and RS occurrence (p = 0.001). Phosphate levels showed the most significant decline post-PN initiation (43%), followed by potassium (19%) and magnesium (17%), primarily within the first 24 hours. No significant associations were found between BMI, fasting duration, unintentional weight loss, or medication history and RS. However, fasting for more than five days (AOR 2.8, 95% CI 0.4–17.7) and ≥10% unintentional weight loss (AOR 1.8, 95% CI 0.4–7.7) increased the likelihood of RS. **Conclusions:** RS is prevalent among adult PN patients, predominantly with mild severity. Pre-existing electrolyte abnormalities, especially in phosphate levels, were robust predictors. Larger studies are needed to better elucidate the associations between risk factors and RS in the local population.

Key Words: parenteral nutrition, refeeding syndrome (RS), occurrence, risk factors, Malaysia

INTRODUCTION

Refeeding syndrome (RS) is a potentially life-threatening condition that can occur when nutritional support is initiated in malnourished individuals.[1-3] It is characterised by severe shifts in fluids and electrolytes, particularly phosphate, potassium, and magnesium, as well as altered glucose metabolism. These changes are primarily driven by the sudden reintroduction of carbohydrates, leading to increased insulin secretion, which shifts electrolytes from the blood into the cells, resulting in potentially fatal complications.[4] Due to the lack of standardisation and precise electrolyte threshold values for RS, previous studies have reported varying incidence rates of RS, ranging from 0% to 80% with this divergence being influenced

by the characteristics of the study population and the vagueness of the criteria used to define RS.[5]

The populations most prone to developing RS include those with chronic malnutrition, such as individuals with anorexia nervosa, chronic alcoholism, prolonged fasting, or severe gastrointestinal diseases. It also affects patients with conditions that result in significant weight loss or those who have undergone prolonged periods of inadequate nutrition, such as elderly patients with frailty or those recovering from major surgery.[6]

The shift from starvation to refeeding triggers an increased cellular uptake of glucose, potassium, phosphate, and magnesium, leading to their depletion in the bloodstream.[3,6] Early signs of RS, typically appearing within the first 72 hours of nutritional therapy, include significantly low blood levels of phosphate, potassium, and magnesium.[7] Severe hypophosphatemia is frequently recognised as a key feature of RS.8 If untreated, these imbalances can result in acute fluid overload, respiratory failure, and heart failure, posing significant risks of morbidity and mortality.[3,8,9]

Several risk factors increase the likelihood of developing RS. According to the National Institute for Health and Care Excellence (NICE) Guidelines,[4] patients who meet the criteria outlined in Table 1 are deemed to be at high risk for developing RS. This high-risk group includes a substantial number of patients requiring parenteral nutrition (PN) therapy. Understanding these factors is essential for the early identification and management of at-risk patients to prevent the potentially severe consequences of this syndrome.

The American Society of Parenteral and Enteral Nutrition (ASPEN) has outlined methods for identifying patients at risk of RS, aligning closely with NICE guidelines. In addition, ASPEN has provided detailed classifications of RS severity, along with strategies for prevention and treatment. ASPEN categorises RS severity as follows: a 10%–20% reduction in serum phosphorus, potassium, and/or magnesium levels indicates mild RS; a 20%–30% reduction suggests moderate RS; and a reduction greater than 30%, or the onset of organ dysfunction within 5 days of initiating nutrition support, signifies severe RS.[10] This classification emphasises the importance of thorough patient assessment to appropriately categorise its severity, enabling tailored management to avert complications. This approach supports close monitoring and the implementation of targeted interventions.

A prospective cohort study conducted in London demonstrated that RS could be predicted with 66.7% sensitivity and over 80% specificity in patients with poor nutritional intake for more than 10 days, weight loss exceeding 15%, and low baseline serum magnesium levels. While no deaths were directly attributed to RS, mortality occurred due to other causes such as

cerebrovascular accidents, severe injuries, respiratory failure, and organ failure during the feeding period (5.3%) and hospitalisation (28%).8 In Malaysia, research on RS is limited. A 2015 study by the International Islamic University Malaysia (IIUM) investigated the incidence of refeeding hypophosphatemia in intensive care unit (ICU) patients, focusing solely on hypophosphatemia and reported that refeeding hypophosphatemia occurs in 45% of ICU patients, with risk factors including a higher Nutrition Risk in the Critically Ill (NUTRIC) score and hypomagnesemia, though no differences in outcomes such as mortality, length of hospital or ICU stay and duration of mechanical ventilation were seen.[11] Due to the lack of RS data in Malaysian population, this current study has been conducted to determine the occurrence of RS and its associated risk factors in hospitalised Malaysian adult patients.

MATERIALS AND METHODS

Study design

This was a retrospective observational study conducted at a single-site university teaching hospital - Hospital Canselor Tuanku Muhriz (HCTM) from October 2023 to December 2023 using a universal sampling method. Inpatients over the age of age 18 years, commencing PN for more than 48 hours, between July 2022 and July 2023 were included in the study. Data were collected through a review of patients' medical records and electronic laboratory records. Since this retrospective study utilised routinely available clinical data, informed consent was not required. Regulatory and ethical approval was obtained from the institutional ethics review board (UKM PPI/111/8/JEP-2023-637), and all individual patient data were anonymised to ensure confidentiality.

Sample size

Using Krejcie and Morgan formula,[12] the estimated sample size was 85 participants. This was estimated from the reported prevalence of the refeeding hypophosphatemia in a Malaysian intensive care unit at a government hospital,[11] being the closest reported data of RS in the local population. However, since a universal sampling approach was used, the calculated sample size served as a guide. All accessible data from medical records that met the inclusion criteria were included.

Data collection

The data collection form that was developed for this study consisted of 5 sections; (i) patient demographic profiles; (ii) laboratory investigations; (iii) risk factors of RS (criteria as

displayed in Table 1); (iv) severity of RS as defined by ASPEN, and (v) complications of RS.[6] The diagnostic criteria used by the research team to confirm RS is based on ASPEN criteria, which is a decrease in any 1, 2, or 3 of serum phosphorus, potassium, and/or magnesium levels by more than 10% of normal values.[10]

Clinical data such as vital signs (blood pressure, pulse, respiratory rate, temperature), electrolyte levels, full blood count, liver function test and renal profile as well as anthropometric data such as weight and height were collected from patient medical records or the hospital electronic inpatient system. Serum electrolyte readings refer specifically to phosphate, magnesium and potassium levels throughout this work, from up to 48 hours prior to PN initiation and up to 72 hours post PN initiation were obtained. Monitoring of electrolytes in this study is based on in-house hospital practice that recommends daily monitoring of electrolyte levels as baseline prior to PN initiation and post PN initiation for 7 days or until stable. This protocol is based on recommendation from international guidelines such as ASPEN and the British Association for Parenteral and Enteral Nutrition (BAPEN).[13,14] Body mass index (BMI) and unintentional weight loss were calculated from anthropometric data, duration of fasting was based on the medical history or recorded days of nil by mouth, and the history of medicines used was based on the medication history records. Severity of RS was determined following the ASPEN criteria of percentage of drop in serum phosphorus, potassium, and/or magnesium levels from before to after PN initiation, up to 72 hours post PN initiation or the onset of organ dysfunction within 5 days of initiating nutrition support.

Data analysis

Data are presented as mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous data; absolute and relative frequency for categorical data, respectively. Differences between groups were computed with t-tests for normally distributed data, Mann-Whitney U for non-normally distributed data, chi-square test for categorical data, multiple binary logistic regression for association between risk factors and occurrence of RS, with a *p*-value ≤ 0.05 indicating significance. To account for potential interactions among factors associated with RS, multiple logistic regression analysis was performed, incorporating key independent variables: BMI, duration of fasting, percentage of unintentional weight loss, and electrolyte levels prior to PN initiation as well as interaction terms (BMI*duration of fasting, BMI*unintentional weight loss, and duration of fasting*unintentional weight loss). To check for multicollinearity, Variance Inflation Factor (VIF) analysis was conducted. A VIF

threshold of >5 was used to indicate high collinearity. The results revealed substantial collinearity between BMI and duration of fasting, with both variables showing VIF values exceeding 5, suggesting redundancy between these variables. To address collinearity, BMI was excluded, and fasting duration was retained in the final model based on better model fit (higher Nagelkerke's R^2). Given this finding, the final logistic regression model was adjusted for duration of fasting, unintentional weight loss, and electrolyte levels prior to PN initiation. The revised analysis aimed to ensure robust statistical estimates without bias introduced by interdependent variables. All data analysis was done using SPSS V.29.0 (Chicago, Illinois, USA).

RESULTS

Demographic profiles of adult patients on parenteral nutrition

A total of 97 patients were eligible to be recruited. Seven were excluded as they did not meet inclusion criteria, therefore a total of 90 patients were analysed (56.7% male) with median age 60.5 years (IQR = 19) and BMI 22.9 kg/m2 (IQR = 6.3) (Table 2). RS patients had a median age of 59.5 years (IQR = 21), while non-RS patients had a median age of 60.5 years (IQR = 20). Out of the 30 RS patients, the number of female patients (n = 17, 56.7%) was higher than male patients (n = 13, 43.3%). In contrast, non-RS patients had a higher number of males (n = 38, 63.3%) than females (n = 22, 36.7%). The average weight was 63.7 kg (SD = 14) for RS patients and 63.4 kg (SD = 13.9) for non-RS patients. The median height for RS and non-RS patients was 162.5 cm (IQR = 9) and 165 cm (IQR = 11) respectively. Based on the weight and height, the BMI was calculated. RS patients had a median BMI of 23.6 kg/m2 (IQR = 6.7) while non-RS patients had a median BMI of 22.6 kg/m2 (IQR = 6.3). Overall, the p-value was > 0.05 for all the demographic variables. Hence, there was no statistically significant difference in the demographic variables between RS and non-RS patients. The health status of the recruited patients is presented in Table 5 (Supplementary Files).

Severity and complication of refeeding syndrome

The total number of patients who developed RS was 30 (33.3%) and the severity of RS was analysed with majority (53.5%) reported as mild RS (Table 3). Only one out of 30 RS patients, reportedly developed a complication related to RS – arrhythmia.

Association between risk factors and occurrence of refeeding syndrome

In the initial logistic regression model, BMI, duration of fasting, unintentional weight loss, and their interaction terms (BMI*fasting duration, BMI*weight loss, and fasting duration*weight loss) were tested but all variables were found to be non-significant ($p > 0.05$) except for electrolyte levels ($p = 0.025$). Additionally, high collinearity was observed between BMI and fasting duration (VIF > 5 for both), indicating that their inclusion together could distort model estimates. To address this issue, the regression analysis was repeated, including either BMI or duration of fasting, but not both. Among the revised models, the model that included duration of fasting as an independent variable was finalised, as it demonstrated a better model fit, indicated by a higher Nagelkerke's $R^2 = 0.187$, suggesting it explained a greater proportion of the variance in RS occurrence compared to the model with BMI, Nagelkerke's $R^2 = 0.126$.

The final adjusted model results (Table 4) remained unchanged from the initial analysis, showing that only electrolyte levels prior to PN initiation remained significantly associated with RS occurrence ($p = 0.001$, adjusted odds ratio [AOR] 6.1, 95% CI 2.0 – 18.4). No significant associations were observed for duration of fasting, or unintentional weight loss, even after adjusting for collinearity.

There was a statistically significant association between pre-existing electrolyte derangements for potassium, magnesium and phosphate with RS occurrence (p = 0.018). The levels of potassium, magnesium and phosphate were analysed and notably, phosphate levels exhibited the most pronounced decline post-PN initiation (43%), followed by potassium (19%) and magnesium (17%). The electrolyte derangements primarily occurred within the initial 24 hours post-PN initiation. The changes were monitored 24, 48 and 72 hours post PN-initiation as shown in Table 6 (Supplementary Files).

Derangement of any of the three electrolyte levels before PN initiation independently predicted RS (AOR 6.1, 95% CI 2.0 – 18.4, p = 0.001); other variables were not significantly associated with RS. However, the likelihood of RS occurring was higher in patients who were fasting more than 5 days (AOR 2.8, 95% CI 0.4 to 17.7, $p = 0.27$) and in patients with $\geqslant$ 10% unintentional weight loss (AOR 1.8, 95% CI 0.4 to 7.7, $p = 0.43$).

DISCUSSION

Evidence on RS in the Malaysian hospitalised patient population is scarce. A recent study from Md Ralib et.al. in 2015 reported refeeding hypophosphatemia in ICU patients at a

tertiary hospital was 44.8%.[11] In our retrospective study, it was observed that 33.3% of adult patients who were on PN, developed RS. There is a lack of global standardisation in diagnosing RS, the reported occurrence in this study fits into the wide variation previously reported in other global studies with occurrence of RS between 0 – 80% by review from Friedli et al.; 0 – 62% by review from Cioffi et al.;[5,15] 25% to 43% from Brazilian hospital studies.[16,17] However, this study used ASPEN guidelines as the diagnostic criteria and focused on the first 48 hours before PN and 72 hours after PN initiation, which is the most critical time for identification of risk as well as the manifestation of RS.[8,10] Previous studies have reported similar challenges with the quality and accuracy of diagnostic criteria from NICE guidelines being poor predictors of RS occurrence.[18]

It was observed that the electrolyte derangement levels in our study were the only significant predictor for the occurrence of RS and similarly was reported in previous studies[17-19] highlighting the importance of monitoring electrolyte levels in patients on PN. Additionally, electrolyte derangements of potassium, magnesium and phosphate levels were seen in being associated with RS occurrence. Patients with more than 10% unintentional weight loss and/or fasting for more than 5 days had higher odds ratio values, suggesting a higher chance of developing RS. Therefore, our findings suggest that patients on PN with more than 10% unintentional weight loss or without dietary intake for more than 5 days have a higher risk for RS as shown by international guidelines.[4,10] The exclusion of either BMI or fasting duration did not alter the overall conclusions, indicating that these variables were not independent risk factors for RS in this study population. The lack of association between BMI, fasting duration, and RS suggests that these factors may act as interdependent proxies for malnutrition, rather than independent predictors.

History taking is essential when initiating patients on PN, as it helps assess nutritional status and identify risks such as RS. A comprehensive review of the patient's dietary intake, recent weight changes, chronic conditions, and history of medication use or substance abuse provides critical data to tailor PN regimens and prevent RS through early identification of RS risk. Identifying risk factors such as prolonged starvation, alcoholism, and significant weight loss enables clinicians to implement preventive measures, including gradual caloric increases, electrolyte correction and monitoring before initiating PN. Additionally, evaluating comorbidities and medications helps address metabolic and electrolyte imbalances that may arise during PN. Effective history taking and medication reconciliation, therefore, plays a pivotal role in reducing RS risk and improving patient outcomes.[20-22]

Awareness and education are critical to ensuring healthcare professionals understand the importance of proper history taking during the pre-initiation review for PN. Healthcare providers may not be fully aware of the key data required to assess the risk of RS or may underestimate its occurrence and potential severity. Structured education and training programs can address this gap by emphasising the role of comprehensive nutritional assessments in identifying at-risk patients, including those with prolonged malnutrition, significant weight loss, or chronic illnesses. By equipping them with the knowledge and skills to gather important dietary, medical, and medication histories during PN pre-initiation review, they can more accurately identify patients vulnerable to RS. This increased focus on education and awareness will ultimately improve patient safety and outcomes during PN therapy.[23,24]

Approximately half of the RS patients (53.3%) had mild RS, defined as 10-20% derangement in either of the three electrolytes, with phosphate levels being the electrolyte that had the most significant drop pre to post PN initiation emphasising previous findings that have recognised hypophosphatemia as the universally recognised hallmark of RS.[23] This finding emphasises the importance of monitoring electrolyte levels in PN patients, particularly within the first 24 to 72 hours after initiating PN, to promptly identify and address early signs of RS. Previous research has underscored the critical need for close daily monitoring of biochemical parameters, particularly during the initial week of nutrition support.[2,3,25]

Only one patient was reported with a RS-related complication, specifically arrythmia. The limited detection of RS-related complications in this case may be attributed to overlapping clinical presentations with other conditions, such as electrolyte imbalances from chronic illnesses or malnutrition, which complicates the identification of RS-specific symptoms. The challenge in distinguishing RS complications from those of other clinical conditions is well-documented, as the clinical presentations often overlap with other critical illness syndromes, making identification of RS complications challenging.[2,6] Moreover, inadequate monitoring specifically for RS complications may have contributed to the underreporting. This aligns with previous studies that suggest serious complications of RS are uncommon and rarely cause death, especially in hospital settings where careful monitoring of electrolyte levels is in place.[25,26] This finding further emphasises the need for heightened awareness and vigilance in identifying RS and its complications.[20]

Strengths and weaknesses of the study

The findings of this study should be interpreted with caution, as it was not designed to investigate the underlying mechanisms of RS. One of the key strengths lies in the use of standardised diagnostic criteria which was to ensure consistency in the identification of cases. However, the study's external validity is limited due to the inherent bias of its narrow selection criteria, being a single-centre study. Additionally, the retrospective nature of data collection resulted in incomplete records and inconsistencies in medical documentation, which led to the exclusion of some potentially eligible patients from the analysis. Furthermore, the risk factors for RS, such as fasting duration, weight loss, and BMI, may interact and act as confounding factors, potentially influencing the association analysis presented in Table 4. In this study, adjustments for confounding effects were made by assessing interaction terms; however, there is still room for improvement.

Future prospective multicenter studies are needed to increase sample size, reduce biases, and improve generalizability, while also incorporating standardized complications monitoring and electrolyte monitoring study protocols based on clinical guidelines to ensure comprehensive data collection. Additionally, advanced statistical approaches, such as stratified analysis or machine learning models, should be employed to refine analyses, enhance confounder adjustments, and better assess multivariable interactions for a more precise understanding of RS risk factors and management.

Conclusion

In conclusion, this study found that the incidence of RS among adult patients at HCTM is 33%. The majority of patients experienced mild RS with minimal RS-related complications. Electrolyte imbalances emerged as the most significant predictor of RS, while unintentional weight loss and fasting duration were identified as clinically important risk factors. Electrolyte disturbances, especially phosphate depletion, predominantly occurred within the first 24 hours of PN initiation, with phosphate reduction being the most prominent marker of RS. Further prospective studies are needed to understand the risk factors associated with RS in this patient population.

ACKNOWLEDGEMENTS

We thank the participation of the subjects in Beijing, China.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no conflict of interest.

This research was funded by the National Natural Science Foundation of China (No.81673146) and CNS Research Fund for DRIs (Grant No. 2021-Water).

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Table 1. Criteria for determining people at high risk of RS[4]

Patient has 1 or more of the following:
BMI less than 16 kg/m^2
Unintentional weight loss greater than 15% within the last 3 to 6 months
Little or no nutritional intake for more than 10 days
Low levels of potassium, phosphate or magnesium before feeding
Or patient has 2 or more of the following:
BMI less than 18.5 kg/m^2
Unintentional weight loss greater than 10% within the last 3 to 6 months
Little or no nutritional intake for more than 5 days
A history of alcohol abuse or drug including insulin, chemotherapy, antacids or diuretics

Table 2. Demographic profiles (n=90)

Demographic variables	All patients (n = 90)	RS patients (n = 30)	Non-RS patients (n=60)	p-value
Age (median, IQR)	(60.5, 52.0 – 72.5)	(59.5, 47.8 – 68.5)	(60.5, 52 - 72)	$p = 0.601^{‡}$
Gender, n (%)				
Male	51 (56.7%)	13 (43.3%)	38 (63.3%)	$p = 0.071^{§}$
Female	39 (43.3%)	17 (56.7%)	22 (36.7%)	
Weight (kg) (mean ± SD)	63.5 ± 13.9	63.7 ± 14.0	63.4 ± 13.9	$p = 0.919^{†}$
Height (cm) (median, IQR)	(165, 160 - 170)	(162.5, 158.8 – 168.8)	(165, 160 – 170.8)	$p = 0.174^{‡}$
BMI (median, IQR)	(22.9, 20.3 – 26.5)	(23.6, 20.2 – 26.9)	(22.6, 20.1 – 26.4)	$p = 0.508^{‡}$

RS - refeeding syndrome; IQR – interquartile range at 25th and 75th percentile; SD - standard deviation.
[†]Independent T-test
[‡]Mann-Whitney U test
[§]Chi-square test.

Table 3. Severity of RS (n=30)

Variables	Frequency (n = 30)	Percentage (%)
Percentage electrolyte reduction K, Mg and/or PO_4		
10 – 20% (mild RS)	16	53.3%
20 – 30% (moderate RS)	7	23.3%
> 30 (severe RS)	7	23.3%

K – potassium; Mg – magnesium; PO4 – phosphate; RS - refeeding syndrome

Table 4. Association between risk factors and occurrence of RS (n=90)

Variables	Multiple Binary Logistic Regression			
	95% CI		p-value	Adjusted OR
	Lower	Upper		
Duration of fasting, n (%)				
≤ 5 days				
> 5 days	0.446	17.7	0.271	2.81
Unintentional weight loss, n (%)				
< 10%				
≥ 10%	0.416	7.72	0.434	1.79
History, n (%)				
Chemotherapy				
Yes				
No	0.108	2.55	0.426	0.526
Insulin				
Yes				
No	0.147	3.29	0.646	0.694
Antacids				
Yes				
No	0.142	2.78	0.539	0.627
Diuretics				
Yes				
No	0.255	2.84	0.792	0.851
Electrolyte Levels before PN Initiation, n (%)				
Normal				
Derangement	2.016	18.4	0.001	6.09

PN – parenteral nutrition.
p-value < 0.05 denotes statistical significance.