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Incidence and clinical predictors of refeeding syndrome among malnourished patients in a tertiary care hospital: A prospective, analytical single-center study

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Abstract

Introduction: Malnutrition is highly prevalent among hospitalized patients and is a known significant risk factor for the development of Refeeding Syndrome (RFS). However, data on the actual incidence and specific clinical predictors of RFS in the Philippines remain scarce. This study aims to determine the incidence of RFS and identify significant clinical predictors of its occurrence in a local tertiary hospital.

Methodology: This prospective, analytical single-center study was conducted at Vicente Sotto Memorial Medical Center (VSMMC) in Cebu City, Philippines, from October 2022 to December 2023. A total of 217 adult patients were screened for malnutrition risk using the Nutrition Risk Screening 2002 (NRS-2002) tool through bedside interview. RFS was defined according to the American Society for Parenteral and Enteral Nutrition (ASPEN) criteria, based on NRS >4 and documented electrolyte changes (hypophosphatemia, hypokalemia, or hypomagnesemia) within five days post-resumption of feeding. Electrolyte levels, daily caloric intake, and protein intake were monitored. Significant risk factors were analyzed using binary logistic regression to ascertain the effect size and predictive utility.

Results: Of the 217 patients screened, 70 (32%) were categorized as high risk for malnutrition and RFS with an NRS 2002 score of at least 4. RFS occurred in 14 patients (20% of the at-risk cohort). Patients with RFS were significantly older (mean age 54.71 + 18.20; p=0.44) and demonstrated significantly lower mean daily total protein intake (41.25 + 12.88 g/day; p=0.01) and lower mean total caloric intake (884.64 + 559.25 kcal/day; p=0.01) compared to the non-RFS group. Serum albumin (2.59 + 0.27 g/dL; p=0.035), phosphorus (1.66 + 0.29 mg/dL; p=0.00), magnesium (1.96 + 0.36 mg/dL; p=0.04) and potassium (3.13 + 0.43 meq/L; p=0.002) were likewise lower among the RFS group. Higher incidence of arrhythmia (50% vs 21%; p=0.003), shock (64% vs 32%; p=0.027), ventilatory support (71% vs 23%; p=0.01) and mortality (64.29% vs 21.43%; p=0.003) were noted in subjects who developed RFS. Binary logistic regression identified advanced age (NRS component) and total protein intake <50g/day as the strongest independent predictors of RFS occurrence.

Conclusion and Recommendations: The incidence of RFS (20%) among at-risk patients in this tertiary care setting was high, indicating that RFS represented a significant cause of in-hospital morbidity and mortality. Advanced age and total protein intake less than 50g/day were identified as crucial, independent predictors. These findings enforced the consistent, mandatory implementation of nutritional risk screening for all admitted patients, especially the elderly, and immediate referral to the Clinical Nutrition Service to ensure rapid, prophylactic, and safely titrated nutritional support.

Keywords: *Refeeding Syndrome, Malnutrition, Hypophosphatemia*

Introduction

Background of the Study

The global burden of malnutrition is significant, with studies demonstrating high prevalence rates among hospitalized patients, particularly those who are critically ill. This state of undernutrition predisposes patients to numerous adverse outcomes, chief among them is the life-threatening metabolic complication known as Refeeding Syndrome (RFS). RFS was first systematically reported in the late 1940s, during the Second World War, when severely undernourished prisoners developed acute neurological and cardiopulmonary disorders upon the resumption of aggressive nutritional support. Despite this long history and recognition as a serious clinical entity, a universal consensus on the definitive diagnostic criteria for RFS remains challenging to establish.[1] Currently, RFS is broadly defined as a fluid and electrolyte imbalance, potentially resulting in organ failure, induced by the overly rapid or inappropriate delivery of nutrition to a severely malnourished patient.[2]

The pathophysiological hallmark of RFS is hypophosphatemia. During chronic starvation, the body enters a catabolic state, resulting in a severe depletion of total-body phosphorus. When carbohydrate-rich feeding is initiated, the subsequent insulin release triggers an abrupt shift into an anabolic state. This metabolic transition necessitates the rapid intracellular uptake of glucose, water, potassium, magnesium, and most critically, phosphorus, for the synthesis of adenosine triphosphate (ATP) and 2,3-diphosphoglycerate (2,3-DPG).[3] With an already diminished total body store, this sudden intracellular flux causes a precipitous drop in serum phosphorus levels. Since phosphorus is essential for ATP-driven energy production and muscle contraction, severe hypophosphatemia (<1 mg/dL) can lead to grave clinical manifestations, including sudden cardiac death, respiratory failure secondary to diaphragm and intercostal muscle weakness, and ventricular arrhythmias.[3] Additional metabolic aberrations, such as hypokalemia, hypomagnesemia, and thiamine deficiency, can also occur, contributing to cellular dysfunction and worsening the risks of respiratory failure and mortality.[4]

Despite the known severe, and often fatal, consequences of RFS, high-quality epidemiological literature is still limited. The lack of standardized definitions and methodology has made it difficult to establish accurate incidence rates globally. Crucially, there is a significant scarcity of published data regarding the incidence and specific clinical risk factors for RFS in the Philippines. Understanding the local context is vital for tailoring effective screening and prevention strategies. This study, therefore, aims to address this critical gap in the local literature. We hypothesize that RFS incidence in the high-risk cohort will exceed 15% and that patient specific factors and nutritional parameters will serve as independent, measurable predictors of RFS occurrence.

Significance of the Study

Despite the seemingly expected occurrence of RFS among hospitalized, malnourished, and critically ill patients, the circumstances under which RFS occurs, the clinical manifestations and the management of these patients are not clear. There is also very little high-quality literature available in the incidence and prevalence of RFS and clinicians caring for vulnerable groups who may require nutritional support are unable to recognize the risk of RFS. The authors aim to determine the incidence of RFS in the local institution and be able to aid clinicians in identifying the possibility of RFS using available and practical clinical parameters.

General Objectives

To determine the incidence of and create a risk scoring model for refeeding syndrome among hospitalized patients initiated on feeding within the first 5 days, from October 2022 to December 2023, at the medical wards, intensive care unit, and emergency department of Vicente Sotto Memorial Medical Center.

Specific Objectives

1. To determine the patient's characteristics, feeding and laboratory data, electrolyte derangements and hospital outcome of patients with refeeding syndrome as to:

    a. Clinical data
        - Age
        - Height in centimeters
        - Weight in kilogram
        - Body Mass Index (BMI)

    b. Nutritional data
        - Nutritional status score based on Nutrition Risk Screening 2002 (NRS-2002)
        - Type of feeding (oral, enteral, parenteral or mixed)
        - Total calories calculated and delivered (kcal/day)
        - Total protein calculated and delivered (g/day)

    c. Laboratory data
        - Serum electrolytes (Phosphorus, Potassium, Sodium, Magnesium)
        - Serum albumin
        - Total lymphocyte count

    d. Outcome data
        - Arrhythmia incidence – (Yes, No, Type)
        - Mechanical ventilation – (Yes, No, Type)
        - Use of vasopressors – (Yes, No, Number of Vasopressors Used, Type)
        - Status on Discharge – (Improved, Expired, Home Against Medical Advice)

2. To identify the risk factors which predict the development of refeeding syndrome

Conceptual Framework

Figure 1. Conceptual Framework of the Study

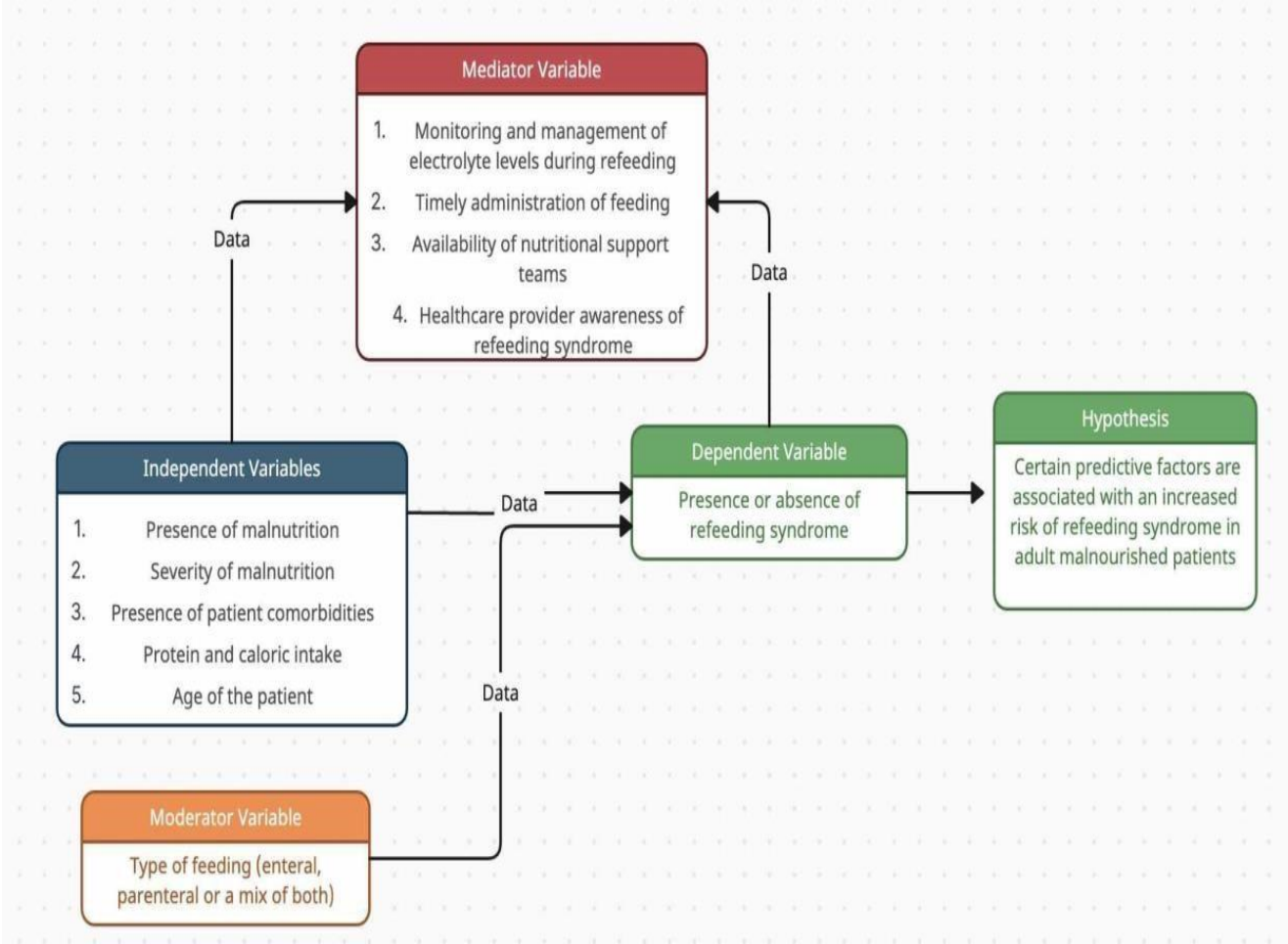


Figure 1 shows the conceptual framework of the study with the identified independent, dependent, mediator and moderator variables.

Review of Related Literature

Refeeding syndrome is a morbid medical condition affecting patients who have not received adequate nutrition and were given high caloric food. High risk patients include underweight and undernourished individuals particularly alcoholics, elderly, homeless, and the seriously ill, such as cancer and post-operative patients.[1,5]

The incidence of refeeding syndrome is not fully known due to a lack of a standard definition.[2] However, various articles about RFS report that its incidence is largely due to a decrease in serum levels of phosphorus.[5,6] The systematic reviews of Friedli et al. (2017) reported an overall incidence of 0-2% but other studies have reported anywhere from 50-80%.

This radical discrepancy in incidence is due to the unclear definition to diagnose RFS.[3]

In the Philippines, very scarce data is available on the prevalence of RFS. Mustofa et al. (2017), however, published a study on Refeeding Syndrome in one of the tertiary hospitals in the Philippines and reported a prevalence rate of 9% in the institution with 90% of patients having hypophosphatemia. The mortality rate is 17%.[3]

Hypophosphatemia is the most common marker and perhaps, the only consistent reliable marker used in RFS. Severe hypophosphatemia has an all-cause mortality of 18.2% compared with 4.6% among patients without hypophosphatemia. Critically ill patients who have had nutrition held for 2 days have a >30% chance of becoming hypophosphatemic. Marik PE et al. (1996) reported in a study in ICU patients that 34% of patients suffered from RFS soon after food was reintroduced at a mean of 1.1 days.[4]

Chen J et al. (2016) addressed the risk factors for RFS in the critically ill population and included one or more of the following: BMI <16, prolongation of insufficient nutrition for more than 10 days, more than 15% weight loss in 3-6 months, and decreased serum electrolyte-vitamin levels before nutrition is started.

Marik PE et al. (1996) performed one of the few prospective ICU studies that attempted to identify risk factors for RFS. The only predictive risk factor for refeeding-related hypophosphatemia was prealbumin <110 g/L.[7] In a similar study by Rio et al. (2013), hypomagnesemia of <0.7 mmol/L was found to be a predictor.[5]

The management principle of RFS is correction of biochemical abnormality and fluid imbalance to reach their normal values if possible. Prevention is the main key in successful management of RFS. Indrarespati et al. (2016) cited 3 main basic factors to prevent RFS: identification of persons at risk, monitoring during feeding, correct regimen of diet.[1] Further research is required to define the most fitting rate at which patients should undergo refeeding. In a study by Brown C et al. (2015), starting the patients at a 1400kcal/day diet seemed to have not increased the occurrence of hypophosphatemia among ICU patients.[4]

Although the 2016 ASPEN/SCCM guidelines suggest that RFS is more common with parenteral nutrition (PN) than enteral nutrition (EN), evidence by Zekei et al. suggests just the opposite. Evidence suggests that it is more common with EN. The likely mechanism is explained by a greater increase in GLP-1 or incretin levels in response to EN. This raises insulin to higher levels than that seen with PN. Permissive underfeeding and reaching caloric goals slowly over 3–4 days by a protocol can decrease complications.

The 2016 ASPEN guidelines endorse hypocaloric parenteral nutrition dosing of ≤ 20 kcal/kg day or eighty percent (80%) of projected energy needs in severely malnourished patients that have contraindications to enteral nutrition over the first seven days of hospitalization in the ICU. Protein necessities should not be reduced.[11] This not only decreases impediments associated with refeeding syndrome, but also decreases hyperglycemia and insulin resistance, frequency of infection, days on ventilation and hospital stay.

Methodology

Study Design, Setting, and Population

This prospective analytical single-center cohort study was conducted at Vicente Sotto Memorial Medical Center (VSMMC) in Cebu City, Philippines. The study period extended from October 2022 to December 2023. A total of 217 adult patients (>18 years old) referred to the Sections of Gastroenterology and Medical Nutrition and admitted to the emergency room, medical wards, and intensive care unit were screened for participation.

Inclusion Criteria

1. >18 years old
2. Assessed to have severe nutrition risk with an NRS 2002 score of ≥4 via bedside interview
3. Baseline phosphate levels of low (2.0 mg/dL and below) during the first 5 days of initiation of nutrition management
4. Hospital stay of at least 5 days to establish the presence of refeeding syndrome when nutrition was initiated
5. Must be given either enteral or parenteral nutrition

Exclusion Criteria

1. Patients not referred to the sections of Gastroenterology and Medical Nutrition
2. Patients on oral nutrition
3. Patients with an NRS 2002 score of 3 and below
4. Patients with no recorded hypophosphatemia after 5 days of initiation of feeding

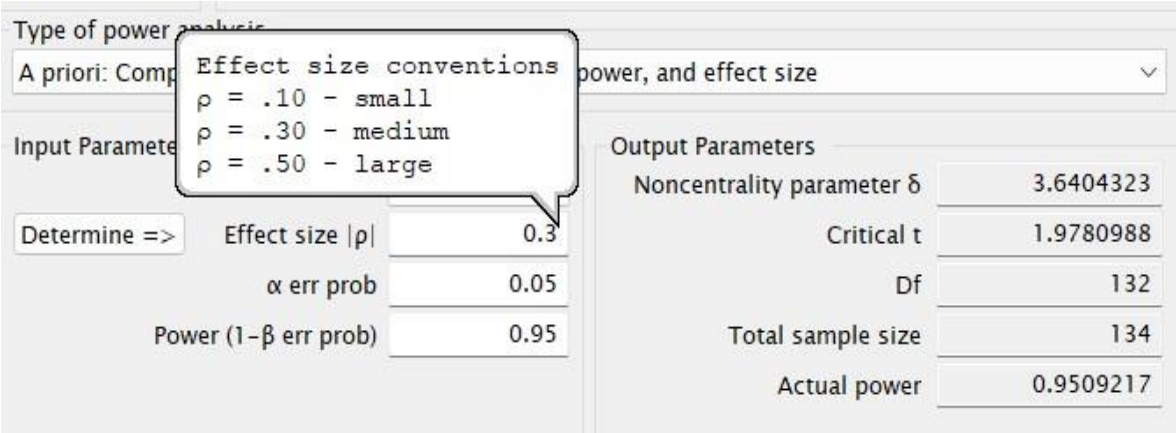
Sampling Procedure

Following the inclusion and exclusion criteria, the study adopted a criterion sampling, a non-probability sampling method of selecting units from a population using a criteria method. Since non-probability sampling does not require a complete survey frame, it is a fast, easy and an inexpensive way of obtaining data.

Sample Size Calculation

Using Gpower, the minimum sample size was computed to be 134 patients for this study to achieve an actual power of 95.1%, with the medium effect size of 0.3, margin of error of 5% and confidence level of 95%. These patients pertain to all enrolled patients referred to and managed by the sections of Medical Nutrition and Gastroenterology under the Department of Internal Medicine that are admitted in the medical wards including the ICU.

Figure 2. Sample Size Computation



Operational Definition of Variables

1. Subjects – adult patients who are malnourished and at-risk to develop refeeding syndrome
2. Factors – demographic or clinical characteristics and laboratory test results of a patient that influence one's probability to develop refeeding syndrome

Data Collection, Experimental Protocol and Monitoring

After obtaining approval from the Institutional Ethics and Review Board (IERB), the hospital administrator, the department chairman of Internal Medicine, and the section head of Gastroenterology to conduct the study, the clinical data of 217 adult patients referred to the Section of Gastroenterology and Medical Nutrition, and admitted to the emergency room, medical wards and intensive care unit starting October 1, 2022, were reviewed. A bedside interview for malnutrition was conducted using the Nutrition Risk Screening 2002 (NRS-2002) scale. A total of 70 patients scored more than 4 in the scale and were diagnosed with severe undernourishment and at risk for refeeding syndrome. Thirty-nine patients on enteral, parenteral or a mix of both were enrolled, while those on oral feeding were excluded from the study. Demographic characteristics such as age, gender, height in centimeters, weight in kilograms, body mass index, type of disease, day of hospitalization, and day of initiation and cessation of feeding were recorded.

Total daily caloric (kcal/day) and protein (g/day) intake were documented daily. Laboratory tests, including serum albumin, total lymphocyte count, creatinine, and electrolyte levels of serum potassium, phosphate, sodium, and magnesium, were taken initially and repeated every 3 to 5 days until discharge. Moreover, clinical outcomes of patients, such as length of hospital stay, use of vasopressors or ventilatory support, occurrence of arrhythmia, and discharge status, were recorded and analyzed.

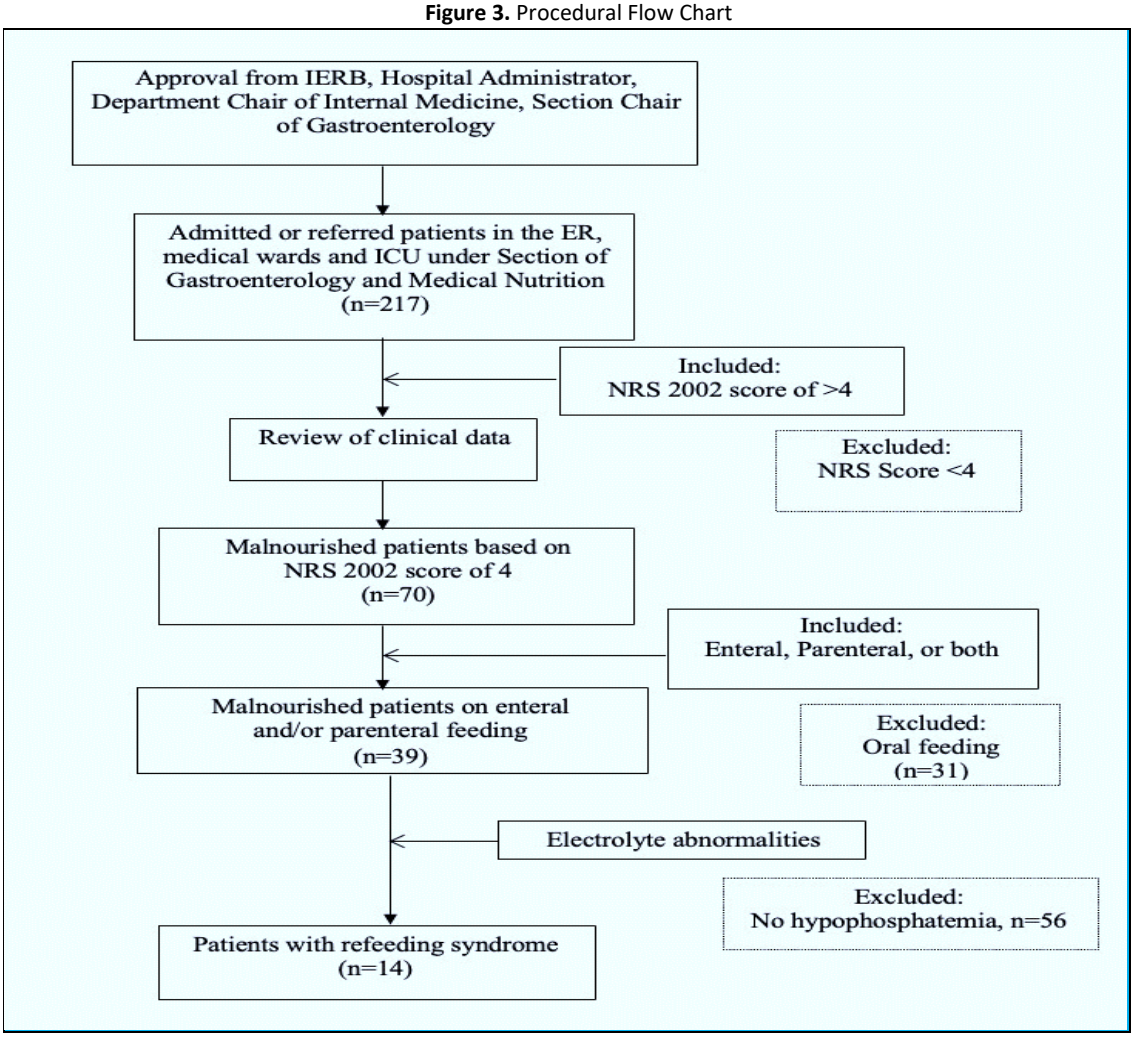
Laboratory tests, such as serum phosphorus and magnesium, were available and were taken free of charge for charity patients. Since enrolled patients were at high risk for refeeding syndrome, taking serum electrolytes was justified.

In the event of non-availability of certain laboratory tests, particularly serum phosphorus, the blood specimen was sent to outside laboratory centers, which the hospital was in partnership with, through the help of the main laboratory and the social service department, at no cost to the patient.

Moreover, although serial blood extraction might give rise to the possibility of developing hematoma, this was prevented by competent, clean, and safe blood extraction by the medical technology team. In case of hematoma in the blood extraction site, protection of the bruised area and application of ice or cold pack were done.

The refeeding protocol followed the standard of care administered by the primary attending physician and the hospital's Clinical Nutrition Service guidelines. This involved a gradual introduction of caloric intake, typically initiating at 50-75% of estimated energy requirements, and slowly titrating upwards.

Figure 3. Procedural Flow Chart



Variables and Outcome Definition

1. Dependent Variable – Occurrence of RFS

    - RFS was defined according to the ASPEN criteria: a patient must be classified as high-risk (NRS-2002 ≥4) and demonstrate a drop in one or more documented serum electrolyte levels (hypophosphatemia, hypokalemia, or hypomagnesemia) within five days post-resumption of feeding.

2. Independent Variables - Clinical and Nutritional Predictors

    - Patient Demographics: Age, Sex, BMI
    - NRS-2002 Components: Scores for Nutritional Status and Severity of Illness
    - Nutritional Intake: Mean daily total caloric intake (kcal/day) and mean daily total protein intake (g/day) over the monitoring period

Data Analysis

The data were analyzed using Minitab software version 21. To determine the patient profiles, categorical data were expressed as frequencies and simple percentages, while continuous ones were expressed as means and standard deviations. To analyze for the significant risk factors in predicting refeeding syndrome, a Chi-square test was used for categorical ones while Pearson rho correlations were performed for the continuous data pairs. All significant factors for the development of refeeding syndrome were subjected to binary logistic regression to ascertain the effect size induced on predicting the binary outcomes. The odds ratio, Beta coefficient, p-value and 95% confidence interval were recorded for this purpose.

To determine for the scoring system in predicting the likelihood of refeeding syndrome, the following model was used:

$$Refeeding\ Syndrome\ (Yes, No) = \beta_1 * Factor\ 1 + \beta_2 * Factor\ 2 + \beta_2 * Factor\ 3 + \cdots + +\beta_n * Factor\ n + Error$$

Where:

$\beta i = the\ coefficient\ of\ the\ binary\ logistic\ regression\ from\ 1\ to\ nth\ variable$

Factor= the risk factors hypothesized in this study to predict refeeding syndrome

Error= y-intercept

To determine the incidence of death (from October 2022 to December 2023) due to refeeding syndrome and all-cause mortality, the formula below was used:

Incidence = number of patients who died due to refeeding syndrome . total number of patients admitted and diagnosed

Risk Scoring Model

To determine significant RFS risk factors that can predict the likelihood of refeeding syndrome, the following model was used:

$$\text{Refeeding Syndrome (Yes, No)} = \beta_1 * \text{Factor 1} + \beta_2 * \text{Factor 2} + \beta_3 * \text{Factor 3} + \ldots + \beta_a * \text{Factor n} + \text{Error}$$

Where βi = the coefficient of the binary logistic regression from 1 to nth variable

Factor = the risk factors hypothesized in this study to predict refeeding syndrome

Error = y-intercept

The parameters needed to be known from the statistical results are the Betas. The Betas came from the odds ratios derived from a binary logistic regression between variables. The logistic coefficient for each of the factors was obtained by taking the natural log of the odds ratio.

The logistic coefficient of each factor was rounded off to the nearest 0.5 or whole number to determine the score. The summation of the scores of factors was taken as the score for that subject. The score with optimal sensitivity and specificity was taken as the cut-off. Positive and negative predictive values were calculated based on this cut-off value. A predictive model was developed to estimate the probability of developing refeeding syndrome based on identified risk factors.

The predictive model was developed to estimate the probability of developing refeeding syndrome based on identified risk factors. The model was validated by calculating the area under the ROC curve (AUROCC) to evaluate the discriminatory power or accuracy of the predictive model. An AUROCC above 0.7 was considered acceptable discrimination, while values above 0.8 were considered good discrimination. Accuracy, sensitivity, and specificity were also calculated to measure the model's predictive ability.

Scope and Limitations

This was a single center study that aimed to identify the incidence of refeeding syndrome in a tertiary public hospital. In a government-owned medical institution, the primary limitation was the availability of laboratory tests, the lack of detailed medical records and the access to enteral feeding.

Ethical Considerations

This investigation was guided by the ethical considerations for conducting research using live humans as participants. The investigator sought the approval of both the hospital administration and the hospital's Institutional Ethics Review Board (IERB) to conduct the study. Collection of data was done only after approval was sought.

A signed informed consent was obtained from the participants prior to start of study. In accordance with the Data Privacy Act of 2012, the confidentiality and anonymity of study participants were preserved while coding was maintained in the study. All participants were identified and assigned a unique alphanumeric identification code. The link of these identification codes was maintained by the investigators and was not disclosed elsewhere.

A Data Extraction Tool was used to record the pertinent data from the patients' charts. The information extracted was encoded through Google Sheets. All data stored in the Google Sheets were destroyed by the Principal Investigator after the finalization of the manuscript. Prior to termination, all data were exported in a password-protected physical hard drive and will be kept in a safety cabinet with lock and key for 10 years. After 10 years, all data in the physical hard drive shall be destroyed by the Principal Investigators. Access to the data collected was restricted only to the investigators of this study and her statistician. In addition, the researcher ensured that no patient names or personal information were included in the study's final report. The researcher guaranteed that only she and her co-author would have access to the data. All information obtained was used exclusively for this study.

This investigation assured that the benefits outweigh the risks, and no funding was sought for this research, and all expenses were incurred by the principal investigator and her co-author. The authors also declared no conflict of interest in the conduct of this study.

Results

The data of a total of 217 adult patients were reviewed. Among these patients, 70 (32%) were malnourished and considered at risk of refeeding syndrome and were, thus, enrolled in the study. Overall, 14 (20%) developed RFS. The review and corresponding analyses were outlined in the following results:

Table 1 shows the clinical characteristics of the patients from two groups. Patients with RFS were relatively older (mean age, 54.71 years old) than the non-RFS subjects (mean age, 50.91 years old).

The body mass indices (BMI) of both patient groups were statistically similar (p>0.05) at 18.86 kg/m^2 for RFS and 18.76 kg/m^2 for non-RFS. In terms of sex distribution, there was a statistical equal distribution (p-value >0.05) of males and females in both groups.

Table 1. Baseline characteristics of patients (n=70)

Variable	RFS (n=14)	Non- RFS (n=56)	P-value
Age (*years*)	54.71 ± 18.20	50.91 ± 15.77	0.44
Male gender (*f*, %)	8 (57.14%)	34 (60.71%)	0.81
Female gender (*f*, %)	6 (42.86%)	22 (39.29%)	0.81
BMI (*kg/m^2*)	18.86 ± 2.95	18.76 ± 1.43	0.85

RS*, refeeding syndrome;* BMI*, body mass index;* f*, frequency;*
Data were reported as x^2 test (f, %) or T-test (mean, SD)

Table 2 shows the total daily protein and caloric intake in both groups. The total protein (g/day) intake of RFS patients was significantly lower (p-value <0.05) at an average of 41.25 g/day than that of the other group who did not have refeeding syndrome at 51.20 g/day. Likewise, the total caloric intake per day significantly differed between the 2 groups (p-value <0.05). The RFS group had a lower daily caloric intake 884.64 kcal/day versus that of the other group at 1275.59 kcal/day.

Table 2. Feeding characteristics of patients (n=70)

Variable	RFS (n_1=14)	Non- RFS (n_2=56)	P-value
Total Protein intake (g/day)[a]	41.25 ± 12.88	51.20 ± 11.02	0.01*
Total Caloric intake (kcal/day)[b]	884.64 ± 559.25	1275.59 ± 295.77	0.01*

g/day, *grams per day*; kcal/day, *kilocalories per day*, **Significant at p-value ≤0.05*
[a]*tested using t-test for 2 independent groups*
[b]*tested using Chi-square test for categorical data*

Table 3 depicts the different laboratory results of patients with refeeding syndrome and with no refeeding syndrome taken within 5 days of initiation of resumption of feeding. Based on this table, it can be validated that the former group of patients had significantly (p-value<0.05) lower serum phosphorus (1.66mg/dL), serum magnesium (1.96mg/dL), serum potassium (3.13mg/dL) and serum albumin (2.59mg/dL) as opposed to the latter. However, serum sodium, creatinine and total lymphocyte count did not show any statistical significance in terms of the mean difference between these groups.

Table 3. Patient's laboratory results (n=70)

Laboratory Characteristics	RFS (n=14)	Non- RFS (n=56)	P-value
Serum Phosphorus (*mg/dL*)	1.96 ± 0.36	2.56 ± 0.40	0.00*
Serum Magnesium *(mg/dL*)	1.96 ± 0.36	2.17 ± 0.35	0.04*
Serum Sodium (*mEq/L*)	133.36 ± 6.96	134.77 ± 8.77	0.57
Serum Potassium (*mEq/L*)	3.13 ± 0.43	3.78 ± 0.72	0.002*
Serum Albumin (*g/dL*) [a]	2.59 ± 0.27	2.78 ± 0.36	0.035*
Serum Creatinine (*mg/dL*) [a]	1.41 ± 0.83	1.60 ± 0.90	0.49
Total Lymphocyte Count (*lymphocytes/µL*)[a]	1659.36 ± 1243.17	1361.56 ± 868.19	0.29

mg/dL, milligrams per deciliter; mEq/L, milliequivalents per liter; µL, microliter

**Significant at p-value ≤0.05*

[a]tested using t-test for 2 independent groups

Table 4 presents the hospital outcomes of the two patient groups. It shows that those who had refeeding syndrome were more likely to develop arrhythmia at 50% than the non-RFS group. Likewise, there was a significantly higher proportion of patients with refeeding syndrome who used mechanical ventilatory support at 71.43% and vasopressors at 64.29%. More patients (64.29%) who had refeeding syndrome died compared to their non-RFS counterpart.

Table 4. Patient outcomes on discharge (n=70)

Outcomes		RFS (n_1=14)		Non- RFS (n_2=56)		P-value
		f	%	*f*	%	
Arrhythmia incidence [b]						
	Yes	7	50	12	21.43	0.03*
	No	7	50	44	78.57	
Mechanical Ventilation [b]						
	Yes	10	71.43	13	23.21	0.01*
	No	4	28.57	43	76.79	
Use of Vasopressors [b]						
	Yes	9	64.29	18	32.14	0.027*
	No	5	35.71	38	67.86	
Status on Discharge [b]						
	Discharge	5	35.71	44	78.57	0.003*
	Expired	9	64.29	12	21.43	

f, frequency; [b]*tested using Chi-square test for categorical data; *Significant at p-value ≤0.05 Data are reported as x^2 test (f, %)*

A binary logistic regression was performed to determine the significant risk factors in the development of refeeding syndrome. Based on Table 5, total protein intake is statistically significant to predict refeeding syndrome (p-value 0.007). Exerting an inverse relationship to RFS, lower total protein intake is associated with a higher likelihood of developing refeeding syndrome. Additionally, low serum magnesium, potassium, phosphorus, and albumin levels also showed statistical significance as factors to predict the likelihood of developing refeeding syndrome.

Since the above risk factors were recorded to have significant negative effects in the prediction of refeeding syndrome, the predictive model is shown as:

– 1.75 * Serum Albumin + *Error*

Table 5. Significant risk factors in the development of refeeding syndrome (n=70)

Risk Factors	Coefficient	Effect	Odds Ratio	P-value
Total Caloric Intake	-0.002	Negative	1.00	0.07
Total Protein Intake	-0.04	Negative	1.00	0.007*
Serum Phosphorus	-2.317	Negative	0.00	0.009*
Serum Magnesium	-1.76	Negative	0.17	0.05*
Serum Potassium	-1.98	Negative	0.15	0.005*
Serum Albumin	-1.75	Negative	0.17	0.007*

Event: *Refeeding Syndrome; *Significant at p-value ≤0.05*

Figure 4 shows that using the predictive model, the AUROCC recorded an accuracy rate of 77.6%. AUROCC above 70% is considered to have acceptable discriminating power to distinguish patients who are likely to develop refeeding syndrome.

Figure 4. The Area Under the Receiving Operating Characteristics Curve (AUROCC)

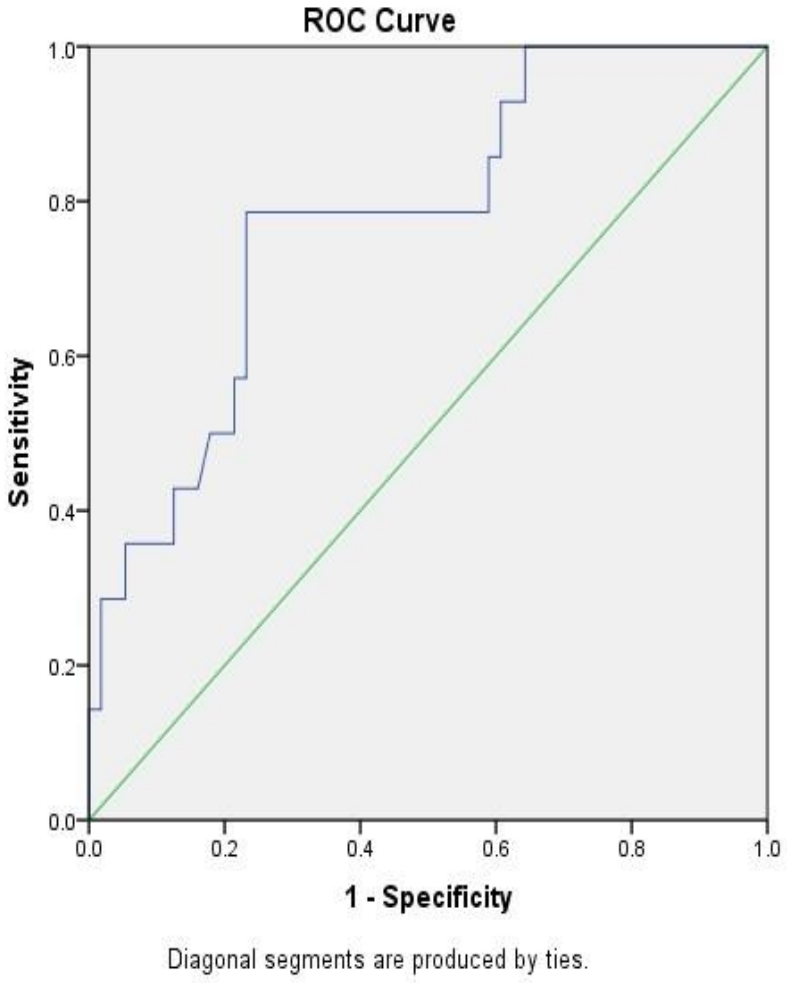


Table 6 shows that the overall accuracy of the predictive model is 77.6%. Moreover, Table 7 illustrates the model output's cut-off value for a passing sensitivity (≥70%) and specificity (≥70%) to determine where the increase in likelihood of refeeding syndrome development already starts. In this table, it shows that the cut-off is set at -10.3180 with a sensitivity of 79% and a specificity of 77%.

Therefore, this predictive Model has acceptable discriminating power to distinguish patients with more likelihood to develop refeeding syndrome.

Table 6. Area Under the Curve (AUC)

Area Under the Curve (AUC)

Test Result Variable(s): Model Output

Area	Standard Error [a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.776	.068	.001	.643	.909

Table 7. Coordinates of the curve

Coordinates of the Curve

Test Result Variable(s): Model Output

Positive if Greater Than or Equal To [a]	Sensitivity	1-Specificity
-10.8251	.786	.429
-10.7723	.786	.411
-10.7140	.786	.393
-10.6480	.786	.375
-10.5600	.786	.357
-10.4500	.786	.339
-10.3180	**.786**	**.304**
-10.2146	.786	.286
-10.1508	.786	.268
-10.1222	.786	.250
-10.0650	.786	.232
-9.9990	.714	.232
-9.9858	.643	.232

Discussion

In this study conducted on 217 adult patients referred to the sections of Gastroenterology and Medical Nutrition, one-third of the patients (32%) were found to be malnourished and at-risk for refeeding syndrome (RFS). Eventually, 20% of the at-risk subjects developed RFS. Additionally, a correlation between the occurrence of RFS and morbidity and mortality were found.

Although, there is uncertainty in the incidence rate of RFS largely due to the diversity of subjects involved in studies and the absence of a universal definition,[12,13] a systematic review by Ciolli et al. (2021), reported that the incidence rate is somewhere between 0 - 80%. Similar to our study, local retrospective research by Inciong J et al. (2014) reported a 30% incidence of Refeeding Syndrome among 30 critically ill, adult patients admitted in a tertiary hospital in Manila, Philippines. Patients who developed RFS had poorer overall outcomes compared to patients who did not develop the syndrome.[11.]

In this study, patients with refeeding syndrome had a lower total protein and caloric intake compared to their non-RFS counterpart. The results are similar to a study by Slingerland-Boot et al. (2023) demonstrating that a significantly lower mean actual protein intake (g/kg/day) was involved in refeeding syndrome in comparison with the patients without refeeding syndrome.[14] The American Society for Parenteral and Enteral Nutrition (ASPEN) emphasized the compact relationship between the caloric and protein intake and refeeding syndrome. In its 2016 recommendations, it stated that protein requirements should not be reduced. Ideal protein intake of critically ill patients was set at 2 g/kg/day to approach nitrogen balance since this subset of patients were hypercatabolic.[14,15,16] Conversely, in this study, patients who had refeeding syndrome had lower caloric intake compared to their non-RFS counterpart.

Although, one study by Shariatpanahi et al. (2022) reported no association between mean actual energy intakes and the occurrence of refeeding syndrome in a cox regression analysis,[14] this was in contrast to a study by Olthoff et al. (2018) where lower caloric intake among RFS at-risk subject was associated with a reduced 6-month mortality risk.[8] Additionally, ASPEN recommended giving hypocaloric parenteral feeding dosing of ≤ 20 kcal/kg/day, equivalent to 80% of estimated energy requirements among malnourished patients.[15]

In the present study, it was shown that lower serum albumin and serum electrolyte levels, particularly serum potassium and magnesium within 5 days of feeding initiation were important risk factors to refeeding syndrome. A similar study by Marik et al. (1996)[7] and Rio et al. (2013)[2] showed that lower albumin, magnesium and potassium levels were predictive factors for refeeding-related hypophosphatemia.

As per hospital outcomes, the refeeding syndrome group in this study had the higher rate of morbidity and mortality compared to its non-RFS counterpart. Among 14 patients who developed hypophosphatemia after resumption of feeding, arrhythmia occurred in 50% of patients compared to 21% in those without hypophosphatemia. Use of mechanical ventilation and vasopressors was also observed in majority of patients with RFS. Moreover, in the RFS group, more than half (64%) expired. This was in stark contrast to the non-RFS group in which the mortality rate was at 21%. In similar studies, patients with confirmed RFS had longer mechanical ventilation use, significantly increased 180-days mortality rates, increased risk for ICU admissions, and longer mean length of hospital stays.[7,12]

Despite the high incidence of refeeding syndrome among critically ill, malnourished patients, there is still a lack of knowledge among clinicians in identifying and managing RFS. To the best of our knowledge, no predictive model exists to aid doctors and other healthcare workers in swiftly identifying patients at-risk. A reliable and efficient predictive tool to anticipate RFS will hopefully bridge the gap between knowledge and timely prevention and effective treatment of this fatal syndrome.

Conclusion

Among admitted patients in this tertiary hospital, 32% were identified to be malnourished based on an NRS score of >4. The incidence rate of refeeding syndrome among at-risk subjects was 20%. Patients with refeeding syndrome had a higher risk of requiring vasopressors and mechanical ventilatory support, developing arrhythmia, and progressing to death. Despite the high morbidity and mortality associated in refeeding syndrome, most clinicians lacked awareness in identifying and managing this syndrome. Parameters such as malnutrition, low total protein intake, low serum electrolyte levels (magnesium, potassium, phosphorus) and low serum albumin should be identified as they predict the development of refeeding syndrome, with high accuracy, sensitivity, and specificity.

Recommendations

Given the high incidence rate and the documented mortality associated with RFS, the authors assert that the syndrome represents a significant and largely avoidable cause of in-hospital mortality. There is an utmost necessity for the consistent and mandatory implementation of a validated nutritional risk screening tool for all admitted patients, specifically to high-risk groups, particularly the elderly, given that advanced age is a significant predictor of RFS development.

It is also recommended that all patients identified as high-risk (NRS >4) must receive an immediate referral to the Clinical Nutrition Service to closely monitor feeding administration, rapidly titrate feeding requirements, and ensure timely and appropriate micronutrient and electrolyte replacement, which are critical steps in preventing the potentially fatal metabolic shifts characteristic of RFS. Additionally, through this research, hospital policy must mandate the implementation of RFS measures, including the adherence to a low-calorie, high-protein initial refeeding regimen, titrated slowly over several days.

Lastly, further analytical studies are recommended to develop and validate a specific local risk prediction score utilizing the identified predictors (age and protein intake) to improve the clinical utility of RFS screening in similar resource-limited settings.

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Appendices

Nutritional Risk Screening Tool

Table 8. Nutritional Risk Screening 2002 (NRS-2002)

Nutritional status	
None	
Mild	Weight loss of >5% in 3 months or 50-75% of the normal food intake in the last week
Moderate	Weight loss >5% in 2 months or BMI 18.5 – 20.5 kg/m2 and reduced general conditions or 25-50% of the normal food intake in the the last week
Severe	Weight loss of >5% in 1 month or 15% in 3 months or BMI of <18.5 kg/m2 and reduced general conditions or 0-25% of the normal food intake in the last week
Advanced age	
	>70 years old

Table 8. (Continued) Nutritional Risk Screening 2002 (NRS-2002)

Severity of the disease (stress metabolism)		
None		
Mild	Hip fracture, chronic diseases especially with complications e.g. liver cirrhosis, COPD, diabetes, cancer, chronic hemodialysis	
Moderate	Stroke, hematologic malignancy, severe pneumonia, extended abdominal surgery	
Severe	Head trauma, hematopoietic stem cell transplantation, Intensive care patients	
Scores		
	0-2 points	Repeat screening weekly
	3-7 points	Patient is at nutritional risk. Nutritional care plan should be set up