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Prevalence of hypophosphatemia and risk of refeeding syndrome in elderly patients admitted to an intensive care unit

Prevalência de hipofosfatemia e risco de síndrome de realimentação em idosos internados em uma unidade de terapia intensiva

Abstract

Introduction: The presence of hypophosphatemia is strongly related to the occurrence of refeeding syndrome in critically ill patients, in which one of the main risk groups is the elderly population. ***Objectives:*** To assess the prevalence of hypophosphatemia and the risk of refeeding syndrome in elderly patients admitted to an intensive care unit. ***Methods:*** Prospective observational study carried out in an intensive care unit with elderly patients of both genders using enteral nutritional therapy. Demographic, clinical and biochemical data were collected, and nutritional screening and assessment were performed. The energy and nutrient requirements were calculated and a cutoff point of 90% was adopted to establish the adequacy of the caloric supply. To assess the risk and occurrence of refeeding syndrome, the criteria proposed by the NICE group were used. Statistical analyses were performed using the SPSS 13.0 program, with a 95% confidence interval (CI). ***Results:*** 44 patients were studied, of which 34.1% were malnourished; 86.4% of patients started enteral nutritional therapy within 48 hours, with 43.2% of caloric adequacy within 72 hours. Hypophosphatemia was found in 9.1% of patients on admission and in 29.5% after starting the diet. Thus, 88.6% of patients had some risk of developing the refeeding syndrome and 40.9% of them manifested the syndrome. ***Conclusion:*** A high prevalence of hypophosphatemia was identified after starting nutritional therapy. In addition, the risk of developing refeeding syndrome was high and its manifestation is similar to data found in the literature.

Keywords: Refeeding syndrome. Hypophosphatemia. Intensive Care Unit. Elderly. Nutritional Therapy

Resumo

Introdução: A presença de hipofosfatemia é fortemente relacionada à ocorrência de síndrome de realimentação em pacientes críticos, na qual um dos principais grupos de risco é a população idosa. ***Objetivos:*** Avaliar a prevalência de hipofosfatemia e o risco de síndrome de realimentação em idosos internados em uma unidade de terapia intensiva. ***Métodos:*** Estudo observacional prospectivo, realizado numa unidade de terapia intensiva com pacientes idosos de ambos os sexos e em uso de terapia nutricional enteral. Foram coletados dados demográficos, clínicos e exames bioquímicos, e realizadas triagem e avaliação nutricional. As necessidades nutricionais foram calculadas e adotou-se o ponto de corte de 90% para estabelecer a adequação da oferta calórica. Para avaliar o risco e a ocorrência de síndrome de realimentação, foram utilizados os critérios propostos pelo grupo NICE. A análise estatística foi realizada com o auxílio do programa SPSS 13.0, com um intervalo de confiança (IC) de 95%. ***Resultados:*** Foram estudados 44 pacientes, dos quais 34,1% estavam em

magreza; 86,4% dos pacientes iniciaram a terapia nutricional enteral em até 48 horas, com 43,2% de adequação calórica em até 72 horas. A hipofosfatemia foi encontrada em 9,1% dos pacientes na admissão e em 29,5% após o início da dieta. Com isso, 88,6% dos pacientes apresentaram algum risco para desenvolver síndrome de realimentação e 40,9% deles manifestaram a síndrome. ***Conclusão:*** Foi identificada elevada prevalência de hipofosfatemia após o início da terapia nutricional. Além disso, o risco de desenvolver síndrome de realimentação foi elevado e sua manifestação se assemelha aos dados encontrados na literatura.

Palavras-chave: Síndrome de realimentação. Hipofosfatemia. Unidades de Terapia Intensiva. Idosos. Terapia Nutricional.

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INTRODUCTION

Hypophosphatemia can be defined as a blood phosphorus concentration of less than 2.5mg/dL. It is considered a rare condition in populations that have a normal diet, as phosphorus can be found easily in foods such as meat, fish, dairy products, nuts and soy. However, when it comes to individuals admitted to hospital units, it happens more frequently, reaching about 3% of patients in the wards and, on average, 30% of patients admitted to intensive care units (ICU).[1,2]

The presence of hypophosphatemia is strongly related to the occurrence of refeeding syndrome in critically ill patients, especially within the initial 72 hours of feeding, with an incidence of 34-52% of this event in critically ill patients.[3-7]

From a pathophysiological point of view, this syndrome occurs after a potentially fatal diversion of fluids and electrolytes, which can occur after the reintroduction of nutrition in predisposed patients. This mechanism depends on the transition from a catabolic to an anabolic state, in which mainly the combustion of carbohydrates provides energy.[8]

During the fasting period, there is a decrease in glucose oxidation, with a preference for protein and fat catabolism to produce glucose and energy. This is due to the decrease in insulin levels, thus depleting glycogen reserves when muscle and liver cells start using fatty acids to maintain normal blood glucose levels. Thus, after starting nutritional therapy, the body returns to using glucose for energy production, leading to an increased demand for inorganic phosphate for the synthesis of adenosine triphosphate (ATP), potassium for the intracellular transport of glucose, magnesium for the synthesis reactions, and thiamine for the oxidation of carbohydrates and amino acids. Such demand causes important intracellular displacement of these substances, whose blood levels can drop dangerously.[9]

One of the main risk groups for the development of the refeeding syndrome is the elderly population, especially those who present or are at risk of developing malnutrition.[10,11] This condition is present in approximately 30-50% of hospitalized patients, of which 20-40% are likely to develop refeeding syndrome.[5] In geriatric patients, the occurrence of refeeding syndrome may be present in 14% of them.[11]

Considering that there is a high prevalence of malnutrition in hospitalized elderly and that this condition is a risk criterion for the development of the refeeding syndrome, and that enteral nutritional therapy is the most used in intensive care, it is essential to assess the frequency of hypophosphatemia and the risk of the occurrence of this syndrome in elderly patients admitted to the ICU, aiming at better monitoring and consequent reduction in mortality in this population.

METHODS

Prospective observational study, carried out from June to October 2019 in the ICU of the Hospital dos Servidores do Estado de Pernambuco. The work was approved by the Ethics and Research Committee of the Universidade Federal de Pernambuco (Federal University of Pernambuco) under CAAE number 10107819.3.0000.5208. Sample selection was performed by convenience, including patients of both genders, aged ≥60 years and using exclusive enteral nutritional therapy. Individuals who had started nutritional support before admission to the ICU or who were using it at home, who had hyperparathyroidism, Fanconi syndrome, or who had undergone kidney transplantation were excluded. The relatives of all participants signed the Free and Informed Consent Term (FICF) before starting data collection.

Demographic and clinical data were collected from the patients' medical records, such as age and sex, diagnosis and comorbidities, type of current treatment (clinical or surgical), type and duration of oxygen therapy, clinical signs and symptoms, medications used and clinical outcomes. Biochemical tests were also performed, which were collected directly from the hospital's electronic system on the day of admission to the ICU and during the first 72 hours after the start of enteral nutritional therapy (ENT).

The biochemical tests investigated and used in the study and their respective cutoff points to characterize normal levels were those established by the hospital laboratory: phosphorus (2.5-4.5 mg/dL), potassium (3-5 mEq/L) and magnesium (1.7-2.6 mg/dL).

All patients were screened within 48 hours of hospital admission using the *Nutritional Risk Screening 2002* tool (NRS-2002), according to which patients with a score ≥3 points were considered at nutritional risk.[12] Nutritional assessment was performed by obtaining the current weight, when possible, or the estimated weight based on the formula by Chumlea et al.,[13] using measures referring to knee height (KH) and arm circumference (AC). Height was obtained from the estimate using the formula by Chumlea et al.[14] or reported by the patient

when possible. These data were used for further calculation of the body mass index (BMI) and classified according to the Lipschitz cutoff points.[15] The AC measurement value was used to calculate its adequacy and subsequent classification according to Kuczmarski, Kuczarisk and Najjar.[16] Calf circumference (CC) was also obtained and classified according to the criteria of Pagotto et al.[17] A weight loss in the last six months was investigated and classified as proposed by Blackburn and Bistrian.[18]

The KH was measured with the patient lying down and with the leg bent at an angle of 90º, using an inelastic measuring tape, positioned from the heel to the anterior surface of the thigh, close to the patella. AC was measured at the midpoint between the acromion of the scapula and the olecranon, determined with the aid of a measuring tape, where, at the time of measurement, the upper limbs were positioned parallel to the patient's trunk. And for CC, the patient was lying down with the leg bent at an angle of 90º, and the measuring tape was positioned at the maximum circumference of the calf, touching the skin without compressing it.

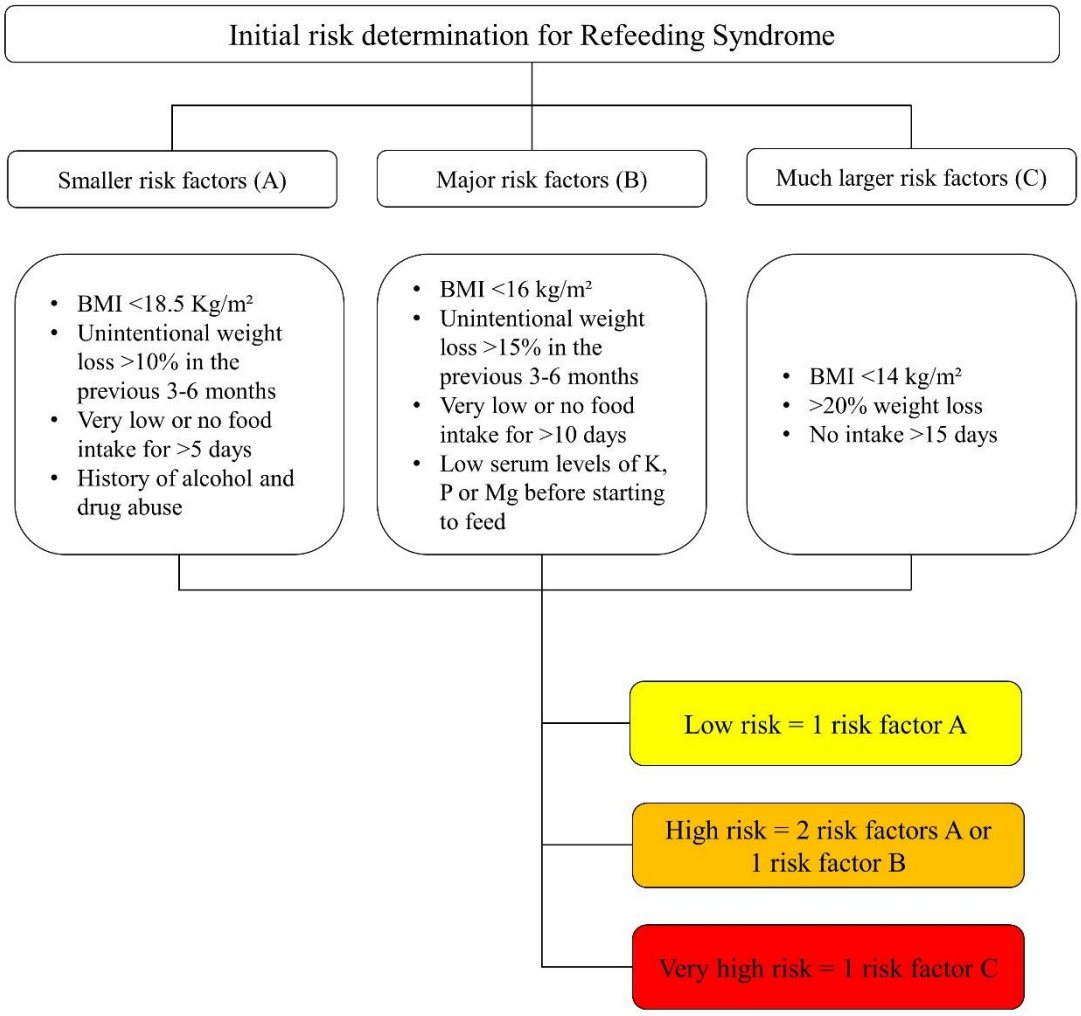
When it was not possible to perform the AC or KH measurements, due to the presence of edema or amputation of the limb that would be measured, or there was no indication to perform the estimated weight, the ideal weight was calculated according to the BMI values adopted by Lipschitz,[15] considering the values of <22Kg/m² for underweight, between 22 and 27Kg/m² for eutrophy and >27Kg/m² for overweight, for later calculation of estimated the energy and nutrient requirements. The nutritional diagnosis was defined by the nutritionist responsible for the ICU based on a complete nutritional assessment.

The caloric intake considered adequate to achieve the nutritional goal was estimated using a practical method, according to the needs of each patient (nutritional status, metabolic status and underlying pathology), as recommended by the main guidelines for nutritional therapy for critically ill patients. The caloric offer was estimated in values ranging from 25-30Kcal/Kg/day, and in obese individuals, it ranged from 22-25Kcal/Kg/day, using the ideal weight. The protein requirement was considered adequate, with values ranging from 1.2-2g/Kg/day.[19,20] As for the volume of enteral diet, the unit's protocol considers as standard the initial offer of 30mL/h on the first day of ENT, progressing the volume within 72 hours to reach the caloric and protein target. If the patient is at risk for refeeding syndrome, the diet is started with reduced volume and progressed slowly to reach adequacy in 5-10 days. Also, after the beginning of ENT, if the patient presents diet intolerance or other clinical manifestations, such as the occurrence of the refeeding syndrome, the volume of the offered diet is reduced and progressed slowly as the condition progresses. Thus, the cutoff point of 90% was adopted to establish the adequacy of the protein and caloric supply.[21]

To assess the risk of refeeding syndrome, the criteria proposed by the *National Institute for Health and Clinical Excellence* (NICE)[22] were used and stratified according to the one proposed by Friedli et al.,[23] as shown in Figure 1,

translated from Aubry et al.[24] Finally, to confirm the presence of the refeeding syndrome, serum phosphate levels were evaluated, in which values less than 2 mg/dL within 72 hours of the onset of ENT and alterations greater than 0.5 mg/dL of reduction in relation to any previous value would be suggestive of the presence of the syndrome.[9]

Figure 1. Criteria for identifying patients at risk for refeeding syndrome.[24]
BMI: Body Mass Index; P: Phosphorus; K: Potassium; Mg: Magnesium.



All information necessary to verify the risk or presence of refeeding syndrome was collected from interviews with family members and/or caregivers at the time of signing the FICF or studied in the medical records of patients who were available within the ICU sector and they were updated daily by the entire multi-professional team at the unit.

Statistical analysis was performed using the SPSS 13.0 (*Statistical Package for the Social Sciences*) program. To assess the behavior of the variables according to the criterion of normality of distribution, the Kolmogorov-Smirnov test was used. Variables with normal distribution were presented as mean and standard deviation. Categorical variables were presented as absolute and percentage values.

RESULTS

Forty-four patients were studied, with a mean age of 75.9±10.6 years, with a minimum age of 60 years and a maximum of 98 years. Sepsis was the most prevalent pathology among the patients studied (45.5%), of which 61.4% required invasive mechanical ventilation. Still, 43.2% of all patients died. Demographic and clinical characteristics are shown in Table 1.

Table 1. Demographic and clinical characteristics of elderly patients admitted to the ICU. Recife-PE, 2019.

Variable	N= 44	%
Sex		
Female	25	56.8
Male	19	43.2
*Diagnóstics**		
Sepsis	20	45.5
Respiratory tract infection	4	9.1
COPD	3	6.8
CKD/AKF	2	4.5
Cancer	4	9.1
Pneumonia	3	6.8
Others	8	18.2
Treatment		
Clinical	40	90.9
Surgical	4	9.1
Comorbidities		
Diabetes mellitus	14	31.8
Hypertension	22	50
Use of Invasive Mechanical Ventilation		
Yes	27	61.4
No	17	38.6
*Invasive Mechanical Ventilation Time***		
< 15 days	21	77.8
≥ 15 days	6	22.2
Use of medications		
Antibiotic	42	95.5
Vasoactive drug	22	50.0
Sedative	28	63.6
Prokinetic	11	25.0
Alcohol or drug abuse		
Yes	8	18.2
No	36	81.8

Table 1. Demographic and clinical characteristics of elderly patients admitted to the ICU. Recife-PE, 2019.(Continues)

Variable	N= 44	%
Clinical Signs within 72h of ENT onset		
Edema	14	31.8
Tachycardia	4	9.1
Tachydyspnea	11	25.0
Clinical outcome		
Hospital discharge	24	54.5
Death	19	43.2
Hospital transfer	1	2.3

COPD: Chronic Obstructive Pulmonary Disease; CKD: Chronic Kidney Disease; AKF: Acute Kidney Failure; ENT: Enteral Nutritional Therapy.
*Only the main medical diagnoses were considered.
**Considering an N of 27 patients on mechanical ventilation

Regarding nutritional status, 43.2% of patients had a history of weight loss, of which 5.3% and 10.5% had significant and severe weight loss, respectively. Regarding the nutritional diagnosis, 34.1% were underweight, 38.6% were eutrophic and 27.3% were overweight (Table 2).

Table 2. Nutritional profile and protein-calorie adequacy of enteral nutritional therapy in elderly patients admitted to the ICU. Recife-PE, 2019.

Variable	N	%
NRS 2002		
At nutritional risk	43	97.7
No nutritional risk	1	2.2
*AC classification**		
Malnutrition	18	46.2
Eutrophy	13	33.3
Overweight/obesity	8	20.5
*CC classification***		
Adequate	9	24.3
Inadequate	28	75.7
Nutritional diagnosis		
Underweight	15	34.1
Eutrophy	17	38.6
Overweight	12	27.3
Weight loss story		
Yes	19	43.2
No	25	56.8
Time to start ENT		
Up to 48 hours	38	86.4
> 48 hours	6	13.6

Table 2. Nutritional profile and protein-calorie adequacy of enteral nutritional therapy in elderly patients admitted to the ICU. Recife-PE, 2019.(Continues)

Variable	N	%
Calorie adequacy of ENT		
Up to 72 hours	19	43.2
> 72 hours	25	56.8
Protein adequacy of ENT		
Up to 72 hours	8	18.2
> 72 hours	36	81.8
Reasons for caloric-protein inadequacy		
Fasting for examination/procedure	11	28.2
Loss of nasoenteral tube	7	18.0
Hemodynamic instability	7	18.0
Regurgitation	5	12.8
Others	9	23.0

NRS 2002: Nutritional Risk Screening 2002; AC: Arm Circumference; CC: Calf Circumference; ENT: Enteral Nutrition Therapy.
**Considering an N of 39 patients who underwent the measurement.*
***Considering an N of 37 patients who underwent the measurement.*

The mean estimate of caloric requirement was 1,733.8±264.5 Kcal/day; and protein, 97.5±20g/day, in which 43.2% of the patients reached caloric adequacy within 72 hours. The main reasons for inadequacy were: fasting for examination/procedure (28.2%), loss of the nasoenteral tube and hemodynamic instability (18.0%) and regurgitation (12.8%) (Table 2).

Mean serum levels of phosphorus, potassium and magnesium at admission were 3.9±1.4mg/dL, 4.3±0.9mEq/dL and 2.0±0.3mg/dL, respectively, with hypophosphatemia being found in 9.1% of patients on admission and in 29.5% within 72 hours after the start of ENT (Table 3). Thus, 88.6% of patients had some risk of developing refeeding syndrome and 40.9% of them manifested the syndrome (Table 4).

Tabela 3. Baixos níveis de eletrólitos na admissão e em até 72 horas após início da TNE em pacientes idosos internados em UTI. Recife-PE, 2019.

Variable	N= 44	%
Admission		
Hypophosphatemia	4	9,1
Hypokalemia	6	13,6
Hypomagnesemia	0	0
After the start of ENT		
Hypophosphatemia	13	29,5
Hypokalemia	8	18,2
Hypomagnesemia	2	4,5

ENT: Enteral nutrition therapy.

Table 4. Risk of refeeding syndrome and syndrome manifestation in elderly patients admitted to the ICU. Recife-PE, 2019.

Variable	N= 44	%
Risk of refeeding syndrome		
Without risk	5	11,4
Low risk	17	38,6
High risk	18	40,9
Very high risk	4	9,1
Manifestation of refeeding syndrome		
Unmanifest	26	59,1
Manifested	18	40,9

DISCUSSION

In recent years, the elderly have been the fastest growing population group in developed and developing countries, largely due to the reduction in the mortality rate, the improvements in economic and social conditions and the continuous advances in medicine.[25] With the aging of the population, there was a significant increase in the number of elderly admissions to the ICU, representing 42-52% of all admissions.[26] Considering this, we emphasize that the NICE study group considers age as a risk factor for refeeding syndrome, and the largest 70 years old with great risk.[9]

Associated with this, there is also a need to investigate the nutritional status of this population, especially in the hospital environment. Literature shows that nutritional screening is essential to identify patients at risk of malnutrition or malnourishment, in addition to managing these nutritional problems.[11] In this study, the NRS-2002 was used, a standard tool used in the nutritional screening protocol of the service where the research was conducted, and from its application, a high prevalence of patients at nutritional risk was observed, drawing attention to the need for adequate and early nutritional support for this audience. Furthermore, an NRS-2002 result of at least 3 points is also shown in the literature as an important risk factor associated with the occurrence of refeeding syndrome.[8,11]

The nutritional status of the elderly population, even in the ICU, is very important in predicting the diagnosis, and malnutrition, the main condition found in the geriatric population, is related to a high risk of complications, such as a greater chance of infections, multiple organ dysfunction, hospitalization prolonged, low quality of life and increased mortality and morbidity.[11,26,27] From this, nutritional assessment is necessary to identify early changes in the nutritional status of the patient. However, in clinical practice, within the ICU, this assessment is difficult or limited due to changes in body composition and difficulty in handling patients, making it necessary to use all available data, such as physical examination, laboratory tests and anthropometry, when possible.[27]

Based on the available methods, it was possible to define the nutritional diagnosis of the studied group, according to which the prevalence of underweight was 34.1%; parameters such as arm and calf circumferences also showed that this population had some deficit in lean mass.[27] This data is similar to that found by Fragas and Oliveira,[28] whose study found a prevalence of malnutrition of 35% in elderly patients.

The presence of hypophosphatemia observed at admission was low, but after the start of ENT, the baseline prevalence values more than tripled. In addition to being one of the main risk factors for the occurrence of the

refeeding syndrome, hypophosphatemia itself is characterized as a risk in critically ill patients, as this condition, when severe, has a mortality prevalence of 18.2% compared to 4.6% among patients without hypophosphatemia.[29]

However, although hypophosphatemia is present in more than 95% of documented cases of refeeding syndrome and is commonly used in clinical practice as a surrogate marker of its occurrence, this practice should not be encouraged, as this deficit is not always related to nutritional intake and the occurrence of the syndrome, which may be asymptomatic.[5]

Considering the high risk of developing refeeding syndrome in hospitalized elderly patients, especially when they need intensive care, mainly due to dietary restriction and non-voluntary weight loss that characterize this period, the present study shows that 88.6% of patients studied had some degree of risk of developing this condition.[10]

The study by Pourhassan et al.,[11] which investigated the relationship between the risk of malnutrition and the risk of refeeding syndrome in the elderly population, showed that, according to the NRS-2002, 74% of patients were at risk of malnutrition and, of these, 75.9% were at high risk of developing the refeeding syndrome. In this study, no such comparison was performed, due to the small sample size, but high prevalences of nutritional risk and risk of developing the syndrome were found.

Olthof et al.,[3] in a retrospective study with 337 critically ill patients in a medical-surgical ICU, found a prevalence of 36.8% of development of the refeeding syndrome, like our results. And Cuskun et al.,[4] in their retrospective study carried out with 117 critically ill patients, found an occurrence of 52.14% of refeeding syndrome. Studies carried out exclusively with critically ill patients to assess the prevalence of refeeding syndrome are scarce, especially when considering elderly patients. Furthermore, due to the lack of a universally accepted definition and diagnostic criteria, there is this variation in prevalence found in different studies on this syndrome.

The refeeding syndrome can occur in all forms of artificial nutrition, but it is more prevalent in patients who use enteral nutrition, followed by parenteral nutrition, due to the stimulation of GLP-1 (*glucagon-like peptide-1*), an intestinal hormone which increases insulin secretion in a glucose-dependent manner, thus increasing intracellular phosphate uptake.[10]

According to national and international consensuses on nutritional therapy for critically ill patients, the recommendation is that it should start within 48 hours of admission, as long as there is hemodynamic stabilization, as it is an extremely important moment in determining the patient's prognosis, and that the caloric goal (considering ≥90% adequacy in this study) is achieved within 72 hours after starting nutritional therapy.[27] This recommendation can be explained by the fact that there is an association between negative nitrogen balance and worse clinical outcomes, despite being a topic still under debate, as some recent studies show the opposite, such as the one carried out by Couto et al.,[30] which identified that there is no association between nutritional adequacy (with a caloric target >70%) in the first 72 hours of hospitalization with worse clinical outcomes and ICU mortality.

In the present study, ENT onset within 48 hours occurred in 86.4% of cases, however, about caloric and protein adequacy, only 43.2% and 18.2% of patients reached the target of 90% within 72 hours, respectively. Understanding that the refeeding syndrome can be potentially fatal and should be considered a serious clinical problem, especially in the elderly population, and that the first 72 hours of starting the diet are considered critical for the manifestation of the syndrome,[10] the guidelines of the NICE[22] group recommend that nutritional therapy starts with a low caloric intake and that the energy target is reached in 5-10 days, according to the individual's risk.

This recommendation shows the importance of risk stratification for refeeding syndrome, as performed in this study. Thus, considering the service's protocol of starting the diet with a low daily volume if the patient is at risk for refeeding syndrome or opting for this strategy after clinical manifestations, such as the presence of signs and

symptoms that characterize the manifestation of the disease, to monitor both the tolerance and the evolution of the patient's condition, the low percentage of caloric-protein adequacy can be explained.

Among the limitations found in this study, the small sample size can be mentioned. In addition, the lack of a single definition for the refeeding syndrome and studies that associate its occurrence in elderly patients and critical elderly patients also made the search for data difficult. However, despite these limitations, we believe that our results can contribute to the current literature, confirming the high risk and high prevalence of refeeding syndrome in critically elderly patients

CONCLUSION

In conclusion, we identified a high prevalence of hypophosphatemia in the study population after starting ENT. Furthermore, we saw that the risk of developing refeeding syndrome is high in the elderly population and that its manifestation is like data found in the literature.

This syndrome can lead to several complications and can be fatal, hence the need to recognize individuals at risk and treat them appropriately and in time, also considering the nutritional therapy that will be used. Thus, the awareness of the entire ICU team regarding this condition and its risks should increase, in addition to the need to implement management protocols for the refeeding syndrome. Further clinical studies are needed to assess nutritional therapy and refeeding syndrome in critically ill elderly patients.

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Contributors

Bezerra AR participated in the conception and design of the study, data interpretation, manuscript writing, review and approval of the final version; Santos PAA participated in the study design, data interpretation and approval of the final version; Santos LS participated in the study design, data interpretation, analysis and review and approval of the final version; Petribú MMV participated in the conception and design of the study, analysis and interpretation of data, review and approval of the final version.

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