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Association between serum lactate levels and refeeding syndrome in critical Ill patients

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ABSTRACT

Aim: To analyze the relationship between blood lactate levels and the development of refeeding syndrome (RFS) in critically Ill patients.

Methods: This prospective cohort study enrolled 141 patients aged 18 years and older who were admitted to the intensive care unit (ICU) of the Hospital Clínica San Francisco for at least 48 hours between January and June 2019. RFS was defined as a 30% decrease in serum phosphorus within 48 hours after the initiation of nutritional support. Serum lactate, SOFA, APACHE II, nutritional risk (NRS-2002), and nutritional status (SGA) were measured upon ICU admission.

Results: 53.8% (n = 83) were male, and 34.8% (n = 49) developed RFS. The primary diagnoses were sepsis and neurocritical conditions, with an overall mortality rate of 18.4%. Among patients with RFS, 85.7% (n = 41) were identified as having a nutritional risk at admission, and 53.1% (n = 26) had moderate malnutrition. Patients with RFS experienced longer ICU stays (12 vs. 7 days, p = 0.006) and longer hospital stays (22 vs. 15 days, p = 0.007) compared to those without RFS. Patients with RFS had significantly higher serum lactate levels compared to those without RFS (1.62 vs. 2.14 mmol/l; p=0.002).

Conclusions: In the present study, serum lactate level is associated with the development of RFS in critically ill patients.

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KEYWORDS

Lactate; Refeeding syndrome; Metabolic rehabilitation; Intensive care unit; Clinical nutrition.

INTRODUCTION

Refeeding syndrome (RFS) is a potentially serious metabolic disorder that occurs when nutritional therapy is initiated after a prolonged period of fasting or significantly reduced nutrient intake[1]. RFS is characterized by electrolytes imbalances, such as decreased phosphate, magnesium, and potassium levels[2]. Symptoms typically occur within 2 to 5 days of refeeding and vary in severity, ranging from asymptomatic or mild to severe, with an increased risk of mortality[1]. This probability largely depends on the patient's degree of malnutrition and the presence of comorbidities.

The absence of a standardized definition and the nonspecific nature of RFS symptoms complicate its diagnosis and make it challenging to determine its prevalence and incidence. Reported prevalence varies widely, from 0.43% to 34% among intensive care unit (ICU) patients[3,4]. In high-risk populations, including patients with severe malnutrition or hospitalized cancer patients, RFS prevalence has been reported at 48% and 25%, respectively[5].

Various criteria have been established over the years to evaluate the risk of RFS, including those from Friedli et al.[6], the American Society of Parenteral and Enteral Nutrition (ASPEN)[7], and the National Committee for Clinical Excellence (NICE)[8]. These guidelines take into consideration common indicators such as body mass index (BMI), percentage of weight loss, previous caloric intake, serum potassium, phosphate, or magnesium levels, and assessment of subcutaneous fat, muscle mass, and associated comorbidities.

Historically, aggressive refeeding has been linked to serious complications. In 1981, the first deaths due to excessive parenteral feeding were reported, and in 1988, severe hypophosphatemia was identified as a primary cause of RFS[9]. This electrolyte imbalance can lead to cardiac dysfunction, neuromuscular disorders, and hematological abnormalities[10,11]. Similarly, severe hypomagnesemia may result in cardiac arrhythmias, neuromuscular disturbances, abdominal discomfort, and seizures[12]. Hypokalemia has been described as a cause of hypotension, cardiac arrest, arrhythmias, gastrointestinal disorders, neuromuscular symptoms, and kidney damage[13].

Lactate is commonly used as a marker of tissue hypoxia[14]. However, in critically ill patients in the acute stage, altered glucose metabolism often leads to elevated lactate levels[15], suggesting a potential relationship between lactate concentrations and the development of RFS. This study aimed to analyze the relationship between serum lactate levels and the onset of refeeding syndrome in critically ill patients.

METHODS

Study design

This prospective, observational, and analytical cohort study was carried out in patients admitted to the ICU of Hospital Clínica San Francisco, located in Guayaquil. The study spanned six months, from January to June 2019.

Subjects

Participants were selected through non-probabilistic convenience sampling. Eligibility criteria included patients aged over 18 with an ICU stay of at least 48 hours and a requirement or indication for nutritional support. Patients with end-stage renal failure requiring dialysis and those with severe hypophosphatemia on admission (<2 mg/dL) were excluded. During the study period, 217 patients were admitted to the ICU, and 141 met the inclusion criteria, forming the study sample. Figure 1 provides a flow chart of the studied population.

Nutritional risk

Nutritional risk was assessed in the first 48 hours of ICU admission using the Nutritional Risk Assessment 2002 (NRS-2002) tool. A score of ≥3 indicating a risk of malnutrition[16].

Nutritional status

Following nutritional risk screening, the nutritional status assessment was carried out by the ICU medical staff using the Subjective Global Assessment (SGA) tool was used to evaluate nutritional status[17]. The SGA classifies patients into three categories: (A) well-nourished, (B) suspected malnutrition or moderate malnutrition, and (C) severe malnutrition, based on

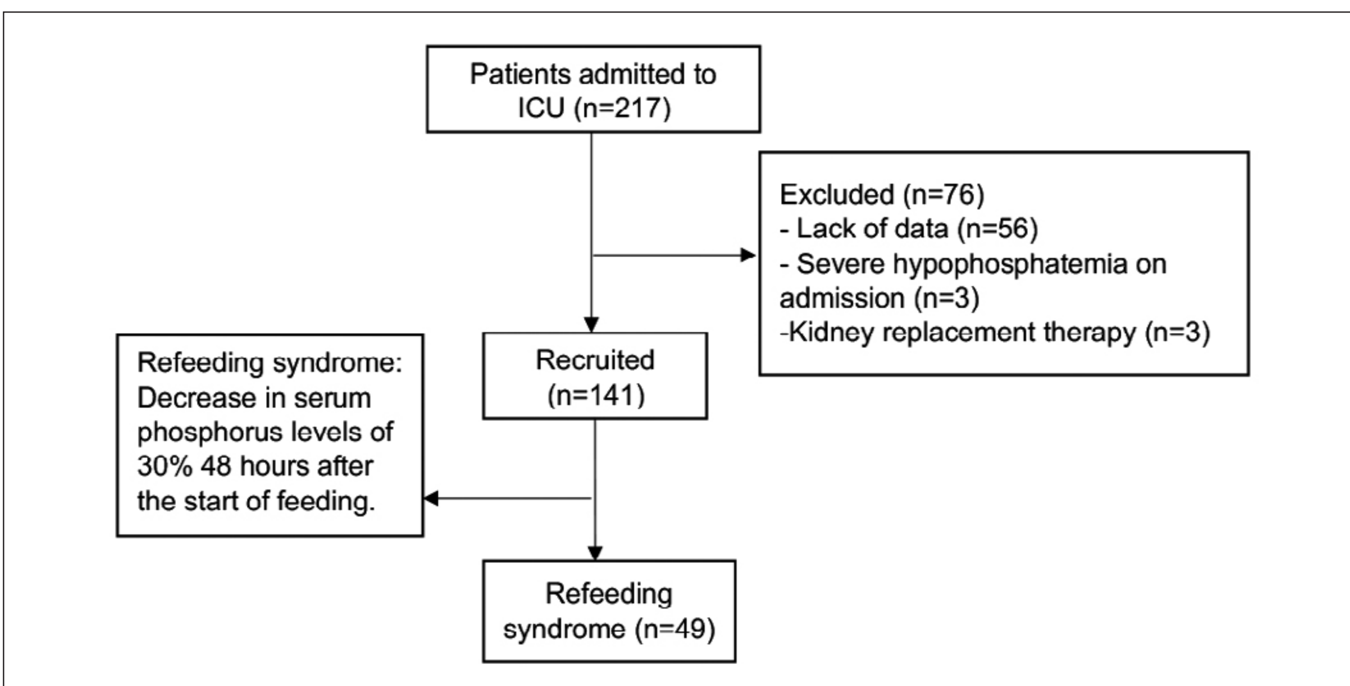


Figure 1. Flowchart of the participants of the study

weight loss, changes in habitual intake, subcutaneous tissue loss, and muscle mass loss.

Severity and mortality

The presence and evolution of multiorgan failure were assessed using the Sequential Organ Failure Assessment (SOFA) score[18], as well as with the Acute Physiology and Chronic Health Evaluation II (APACHE II)[19] to classify the disease severity and predict patient mortality. These assessments were performed within the first 24 hours of ICU admission.

Refeeding syndrome definition

Prior to initiating nutritional support (oral, enteral, or parenteral), plasma levels of phosphorus, potassium, and magnesium were measured and then monitored daily for the first four days of ICU admission. Refeeding syndrome (RFS) was defined as a decrease in serum phosphorus levels of at least 30% within 48 hours of initiating nutritional support, following the ASPEN 2020 criteria[7]. Serum lactate was measured at ICU admission using spectrophotometry.

Statistical analysis

Data for this study were collected from the hospital's electronic medical records and subsequently compiled into an Excel file. Statistical analyses were conducted using SPSS version 24 for Windows. All variables were summarized using descriptive statistics. Qualitative variables are expressed as counts (percentages), and quantitative variables were expressed as means ± standard deviation (SD) or as medians with their respective ranges, depending on the distribution. For comparisons between patients who develop refeeding syndrome and those who do not, Student's t-test, Mann-Whitney U test, or Wilcoxon test were used as appropriate. A p-value of <0.05 was considered statistically significant.

Ethical considerations

Clinical and laboratory data were extracted from the hospital's computerized clinical history system. Informed consent was secured from each patient before their admission to the ICU, and authorization was granted by the institution to conduct the study.

Results

The mean age of the patients was 64 ± 18.8 years, ranging from 21 to 96 years, with 53.8% (n = 83) being male. The primary causes of ICU admission were sepsis (33.3%, n = 47) and neurocritical diseases (17.7%, n = 25). Hypertension was the most common comorbidity, present in 55.3% of patients. The average ICU stay was 8.6 ± 11.1 days, and the average hospital stay was 17.6 ± 15.3 days, with a maximum stay of 93 days. The mean APACHE II score was 11.8 ± 6.3, with an estimated mortality of 15%. The mortality rate at discharge was 17.7% (n = 25). Invasive mechanical ventilation was used in 22% (n = 31) of patients.

Oral nutrition was the most common feeding method, used in 54.6% (n=77) of patients, followed by enteral nutrition (39%, n=55) and parenteral nutrition (7.8%, n=11). Only one patient received a combination of nutritional support methods.

RFS was observed in 34% (n = 49) of the sample. The demographic and clinical characteristics of patients with and without RFS are shown in Table 1. Patients with RFS had a significantly longer ICU stay (12 ± 9.1 vs. 7 ± 5.3 days; p = 0.006) and higher SOFA and APACHE II scores than those without RFS (Table 1). Among patients with sepsis, those who developed RFS had a higher median SOFA score than those without RFS (6.25 vs. 4.50; p = 0.017).

In the RFS group, 85.7% (n = 42) were identified as having nutritional risk upon ICU admission, while 26.5% (n = 13) were classified as having severe malnutrition according to SGA criteria. The most common feeding method among patients with RFS was enteral nutrition (55%), followed by oral feeding (34.6%, n = 17). Of the 11 patients who began parenteral nutrition, 5 developed RFS. The mean values for phosphorus, potassium, magnesium, and lactate at admission were 3.7 ± 1.1 mg/dL, 4.3 ± 3.2 mg/dL, 1.9 ± 0.4 mg/dL, and 1.6 ± 0.9 mmol/L, respectively (Table 2). A statistically significant difference in serum lactate levels at admission was found between patients with and without RFS (1.6 vs. 2.1 mmol/L; p = 0.002), as illustrated in Figure 2.

DISCUSSION

This study describes the association between serum lactate levels upon ICU admission and the onset of RFS. Our results indicate a significant association between these variables, though similar data are not yet reported in the scientific literature.

The association between lactate levels and RFS observed in our study could result from altered thiamine metabolism, a characteristic of this syndrome[20]. Thiamine (vitamin B1) is essential in its active form as a cofactor in converting pyruvate to acetyl-CoA before entering the tricarboxylic acid cycle for ATP production[21]. Thiamine deficiency, often present in malnutrition and alcohol use, can also arise from factors such as advanced age[22], comorbidities (e.g., liver dysfunction, heart failure), surgery (e.g., bariatric), acidosis, sepsis, trauma, high carbohydrate load[23], and RFS. All of these factors may coexist in critically ill patients[24], reducing thiamine levels[25].

In critical ill undergoing refeeding, a lack of thiamine impairs aerobic metabolism, leading to insufficient ATP produc-

Table 1. Demographic, Clinical Characteristics, and Outcomes of patients with and without Refeeding Syndrome

Variables	Total (n = 141)	No RFS (n = 92)	RFS (n = 49)	p-value
Sex, n (%)				
Female	58 (41.1)	35 (38)	23 (46.9)	0.024*
Male	83 (58.9)	57(61.9)	26 (53.1)	0.035*
Age (years), mean ± SD	64 ± 18.8	70 ± 19.4	63 ± 15.1	0.038*
Diagnostic categories, n (%)				
Sepsis	47 (33.3)	29 (31.5)	18 (36.7)	0.043*
Neurocritical Patients	25 (17.7)	12 (13)	13 (26.5)	0.003*
Cardiovascular	30 (21.3)	24 (26.1)	6 (12.2)	0.035*
Hypovolemia	13 (9.2)	9 (9.8)	4 (8.16)	0.670
Trauma	13 (9.2)	9 (9.8)	4 (9.16)	0.670
Oncological	13 (9.2)	6 (6.5)	7 (14.3)	0.541
Comorbidities, n (%)				
Hypertension	78 (55.3)	51 (55.4)	27 (55.1)	0.678
Type 2 diabetes	44 (31.2)	29 (31.5)	15 (30.6)	0.879
Acute myocardial infarction	13 (9.2)	7 (7.6)	3 (6.1)	0.768
ND-CKD	8 (5.7)	8 (8.6)	2 (4.1)	0.051
Cirrhosis	11 (7.8)	5 (5.4)	6 (12.2)	0.040*
Discharge Status, n (%)				
Alive	116 (82.3)	76 (82.6)	40 (81.6)	0.721
Deceased	25 (17.7)	16 (17.3)	9 (18.4)	0.863
ICU Readmission	11 (7.8)	6 (6.5)	5 (10.2)	0.049*
APACHE II Score, mean ± SD	11.8 ± 6.3	11 ± 6.9	14 ± 5.8	0.008*
SOFA Score, mean ± SD	2.1 ± 1.9	1 ± 1.3	3 ± 1.1	0.019*
ICU Stay (days), mean ± SD	8.6 ± 11.2	7 ± 5.3	12 ± 9.1	0.006*
Hospital Stay (days), mean ± SD	17.6 ± 15.3	15 ± 12.9	22 ± 15.2	0.007*
Mechanical ventilation, n (%)	31 (22)	18 (19.6)	13 (26.5)	0.032*
Nutritional Risk, n (%)				
No Risk	36 (25.5)	29 (31.5)	7 (14.3)	0.030*
At Nutritional Risk	105 (74.5)	63 (61.9)	42 (85.7)	0.045*
Nutritional Status, n (%)				
Well-nourished	39 (27.6)	29 (38)	10 (46.9)	0.030*
Moderate malnutrition	78 (55.3)	52 (61.9)	26 (53.1)	0.025*
Severe malnutrition	24 (17)	11 (11.9)	13 (26.5)	0.009*

*p < 0.05.
RFA, Refeeding syndrome; SD, Standard deviation; ND-CKD, Non-dialytic chronic kidney disease; ICU, Intensive care unit.

Table 2. Biochemical Markers over the first four days of Refeeding Syndrome

Biochemical Markers	Day 1	Day 2	Day 3	Day 4
Phosphorus (mg/dL)	3.7 ± 1.1	3.4 ± 0.8	3.1 ± 1.0	3.0 ± 1.0
Potassium (mg/dL)	4.3 ± 3.2	4.0 ± 0.6	3.9 ± 0.7	4.0 ± 3.7
Magnesium (mg/dL)	1.9 ± 0.4	1.9 ± 0.4	1.9 ± 1.8	0.3 ± 0.3

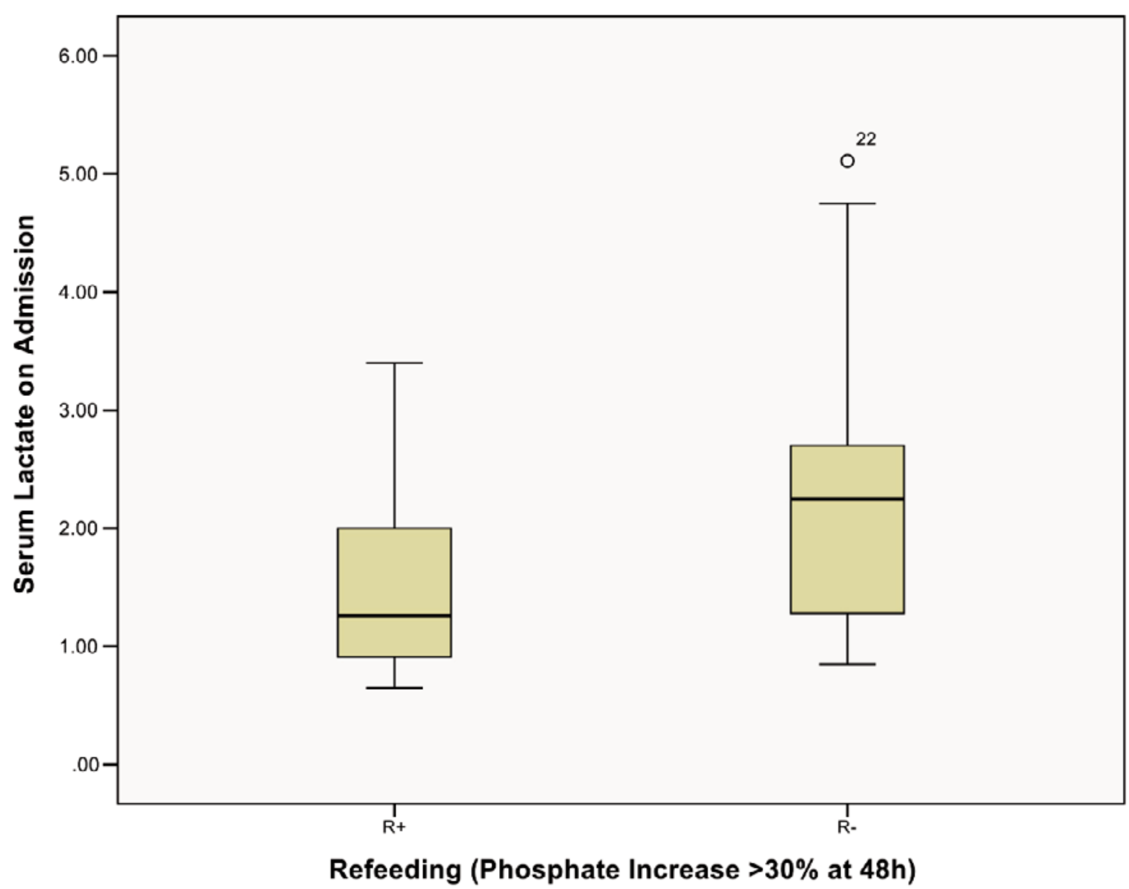
Values are presented as means ± standard deviations.

tion[26]. Consequently, pyruvate is converted to lactate in the absence of thiamine as a cofactor for the Krebs cycle, resulting in hyperlactatemia and metabolic acidosis.

On the other hand, hypomagnesemia has been reported as a common condition even in non-critical patients[27]. In this study, we found a significant decrease in plasma magnesium levels over the first four days of RFS.

The prevalence of RFS in this study was 34.7%. However, de Vargas et al. reported a 43.3% prevalence of RFS in patients on parenteral nutrition in a Brazilian hospital[28]. In contrast, Coşkun et al. reported a 52.1% prevalence of RFS in ICU patients receiving parenteral and enteral nutrition[29].

Symptoms of RFS usually appear within 2 to 5 days of refeeding and vary in severity based on preexisting malnutrition and comorbidities[4]. Monitoring serum phosphorus levels is thus essential for early RFS detection. In a study by Goyale et al., a 30% decrease in baseline phosphorus levels was observed 36 hours after initiating parenteral nutrition, with an RFS prevalence of 62%[30]. Olthof et al., however, reported a 36.4% incidence of RFS in critically ill patients, defining it as hypophosphatemia (<0.16 mmol/L below 0.65 mmol/L) within 72 hours of starting nutritional support[26].



R+: Patients with Refeeding Syndrome; R-: Patients without Refeeding Syndrome.

Figure 2. Serum lactate levels upon admission in patients with and without refeeding syndrome

Gonçalves et al. found a significant a strong negative correlation between thiamine and lactate in patients with diabetes (r= −0.711, p=<.001) and a moderate negative correlation in critically ill patients without diabetes (r = −0.489, p=<.001)[31]. Additionally, Moskowitz et al. observed an inverse relationship between thiamine and lactate levels (p=0.002) in a cohort of 38 patients with diabetic ketoacidosis[32]. Although these findings are relevant, there is no existing evidence specifically linking lactate levels and RFS.

Our study found a statistically significant association between serum lactate levels and RFS, particularly with lactate levels exceeding 2 mmol/L. Although we used the same RFS definition as Goyale et al.[30], differences in nutritional support types aligned with findings by Coşkun et al.[29] However, contrasting results were observed by Zeki et al., who reported a higher RFS incidence in patients on enteral rather than parenteral nutrition[33].

Patients who developed RFS in this study had significantly longer ICU stays. The pooled length of stay in patients with RFS has been reported at 25.5 (95% CI, 20.2-30.9) days[34]. Coşkun et. al also reported longer ICU stays (median: 12 [3–68] vs. 8.5 [3–41] days; p=0.025) and higher mortality in RFS patients (p=0.037)[29]. Nonetheless, in the present report, no significant differences in mortality or ICU stay were observed. Olthof et al. likewise found no significant differences in mortality or median ICU stay between patients with and without RFS, although they noted a non-significant trend toward shorter hospital stays (28 vs. 24 days; p=0.066)[26].

In our study, patients with RFS had significantly higher APACHE II scores. Nevertheless, this difference lacks clinical significance, as it reflects a similar estimated mortality percentage. Coşkun et al., in a retrospective ICU study involving enteral and parenteral nutrition, also found no significant difference in APACHE II scores between patients with and without RFS[29].

A higher SOFA score (6.2 vs. 4.5; p=0.017) was observed in patients with sepsis and RFS compared to those without RFS. In a related observational study on adults receiving enteral nutrition, 42.6% of patients developed RFS and demonstrated higher SOFA scores compared to those without RFS (0.9 ± 0.7 vs, 0.6 ± 0.7)[35]. In addition, Tongyoo et al. found that a SOFA score >12 was associated with reduced RFS risk (OR = 0.45; 95% CI = 0.23-0.88; p = 0.020)[36].

This study has several limitations, including the absence of standardized ICU nutritional support protocols and caloric targets for the studied population. Additionally, patients were not categorized into clinically relevant subgroups, which limits analysis of factors contributing to differences between RFS and non-RFS patients. The study's retrospective design and relatively small sample size also limit the generalizability of findings to other populations with sepsis and RFS. These limitations highlight the need for larger prospective studies with randomized groups and well-defined inclusion criteria to better identify and understand RFS in critically ill patients.

This study is the first to examine the relationship between serum lactate levels and RFS development. Likewise, it provides relevant information on prognostic indicators and disease severity in RFS patients, which can serve as a reference in the clinical and nutritional management of critically ill patients.

CONCLUSION

RFS is a common and serious complication in critically ill patients, linked to higher rates of morbidity and mortality. Sepsis, malnutrition, nutritional risk at admission, and the type of nutritional support appear to be significant risk factors for RFS development. Our findings indicate a prevalence of RFS that is notably higher than reported in general malnutrition literature. Enteral nutrition was the most common form of support among patients with RFS, followed by oral and parenteral feeding. Additionally, patients who developed RFS had significantly longer ICU stays, higher SOFA and APACHE II scores, and higher mortality rates compared to those without RFS. More studies with larger sample sizes are required to generalize these findings.

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