ORIGINAL PAPER

DOI: http://dx.doi.org/10.15403/jgld-4823

Frequency and Related Risk Factors of Refeeding Hypophosphatemia in Patients with Liver Cirrhosis: A Pilot Study

Gulten Can Sezgin[1], Nurhayat Tugra Ozer[2], Gulsah Gunes Sahin[2], Serap Sahin[2], Mustafa Alper Yurci[1], Kadri Guven[1], Kursat Gundogan[2,3]

1) Department of Gastroenterology, Erciyes University, Faculty of Medicine, Kayseri;
2) Department of Clinical Nutrition, Erciyes University, Health Sciences Institute, Kayseri;
3) Department of Medical Intensive Care Unit, Erciyes University, Faculty of Medicine, Kayseri, Turkey

Address for correspondence:
Gulten Can Sezgin, MD. Erciyes University, Faculty of Medicine, Department of Internal Medicine, Division of Gastroenterology, Kayseri, Turkey. 38039, Melikgazi, Kayseri, Turkey
gcsezgin@erciyes.edu.tr

Received: 23.01.2023
Accepted: 14.06.2023

ABSTRACT

Background & Aims: Refeeding hypophosphataemia (RH) is associated with poor clinical outcomes and mortality rates. However, the presence of RH in patients with cirrhosis remains unknown. This study aimed to determine the relationship among the frequency of RH, nutritional status, and disease severity in patients with liver cirrhosis.

Methods: This prospective study was conducted at a single-centre gastroenterology clinic. Malnutrition was identified using the Subjective Global Assessment (SGA). Disease severity was defined using the Child-Turcotte-Pugh (CTP) and the Model for End-Stage Liver Disease (MELD) scores. Hypophosphatemia was defined as a serum phosphate level of <2.0 mg/dL.

Results: Twelve of 50 cirrhotic patients (24%) had RH during hospitalization. The most common RH was determined in four patients on day four during the study follow-up. The sharpest decline in serum phosphate levels was observed on day four (median: 2.3 mg/dL). The CTP score and MELD scores did not differ significantly between RH and non- RH groups ((p=0.478 and p=0.643), respectively. The rate of malnutrition according to the SGA was 56.0%. A total of 82%, 4%, 8%, and 4% of participants received regular diet and oral nutritional supplements, only enteral tube feeding, only parenteral nutrition, and combined enteral and parenteral nutrition, respectively. In the RH group, 32% of participants received only parenteral nutrition and had a higher prevalence of RH than that of patients receiving only oral or enteral tube feeding (p=0.001). The CTP score strongly and negatively correlated with serum phosphorus levels on days two (p=0.016), three (p=0.050), and seven (p=0.017) in the RH group.

Conclusions: This study showed that artificial feeding (enteral or parenteral nutrition) carries a significant risk in terms of RH. Malnourished patients with liver cirrhosis who received parenteral nutrition were closely monitored for a high risk of RH. The CTP score strongly and negatively correlated with serum phosphorus levels.

Key words: cirrhosis – nutrition – hypophosphatemia – refeeding – refeeding hypophosphatemia.

Abbreviations: CTP: Child-Turcotte-Pugh; EN: enteral nutrition; MELD: Model for End-Stage Liver Disease; PN: parenteral nutrition; RFS: recurrence-free survival; RH: refeeding hypophosphatemia; SGA: Subjective Global Assessment.

INTRODUCTION

The liver plays an essential physiological role in nutrient digestion and metabolism. In patients with liver cirrhosis, liver function is impaired and protein-calorie malnutrition is observed [1]. Malnutrition is a common condition in approximately 45–90% of hospitalised cirrhotic patients and can range from mild malnutrition to lean body [2, 3].

Refeeding syndrome is defined as severe fluid and electrolyte shifts in malnourished patients during oral, enteral, or parenteral refeeding [4]. The modern definition of refeeding syndrome is life-threatening, with severely low serum electrolyte concentrations, fluid and electrolyte imbalance, and disturbance of organ function resulting from over-rapid or unbalanced nutrition support [5]. Hypophosphatemia is the most prominent biochemical disorder in refeeding syndrome and is defined as refeeding hypophosphatemia (RH) [6].

Patients with liver cirrhosis and high-risk malnutrition may be at risk of RH. It is a life-threatening constellation of cardiovascular, pulmonary, hepatic, renal, neuromuscular, metabolic, and haematological abnormalities that occur following appropriate alimentary resuscitation in severely malnourished or starved individuals [7]. The risk of developing refeeding syndrome may increase among malnourished patients with malnutrition [8]. Refeeding hypophosphatemia may be overlooked when refeeding liver cirrhosis patients are admitted to a gastroenterology clinic. This metabolic imbalance can result in poor clinical outcomes. Guidelines for preventing and treating refeeding syndrome advise identifying at-risk individuals, controlling hypocaloric nutritional treatment, and replacement of electrolytes [5].

This study aimed to determine the frequency of RH, the relationship between RH and nutritional status, and the clinical characteristics of patients with liver cirrhosis in a gastroenterology clinic.

METHODS

This prospective study was conducted at the Gastroenterology Clinic of our University Hospital and approved by the local Ethics Committee (2019/95). Patient inclusion criteria were as follows: a) patients with liver cirrhosis; b) age >18 years; and c) expected length of hospital stay of at least 48 hours. Pregnant women and those with chronic renal failure (glomerular filtration rate of <60 mL/min) were excluded.

All the patients were followed-up for the first 14 days after hospital admission. Baseline characteristics, including patient age, gender, body mass index, and reason for admission, were recorded. The severity of liver disease was defined using the Child-Turcotte-Pugh (CTP) score based on clinical (ascites and encephalopathy) and laboratory (albumin, bilirubin, and international normalised ratio) parameters and the Model for End-Stage Liver Disease (MELD) score [9, 10]. Malnutrition was determined by the Subjective Global Assessment (SGA), according to self-reported study participants by a clinical dietitian [11, 12]. The daily calorie intake of the patients and type of nutrition (regular diet and/or oral nutritional supplement, enteral nutrition (EN) via a feeding tube, and parenteral nutrition [PN]) were recorded during follow-up. We considered the type of nutrition as the most common nutritional support given for each participant during the study period. A clinical dietitian collected the dietary records of patients who were orally fed each day. We described artificial nutrition as enteral or parenteral feeding.

Data were analysed using Nutrition Information System (BeBis) software (EBISpro for Windows, Stuttgart, Germany). The Harris-Benedict equation calculates the daily calorie target of patients using ideal body weight, according to the European Society for Clinical Nutrition and Metabolism guidelines on clinical nutrition for liver disease [13].

Serum phosphate, magnesium, potassium, and albumin concentrations were recorded during the first 14 days of hospitalisation. Refeeding hypophosphatemia was defined as a decrease in serum phosphate to <2.0 mg/dL (0.65 mmol/L) [6, 14]. Hypopotassemia was defined as a serum potassium level of <3.5 mmol/L, and hypomagnesaemia was defined as a serum magnesium of <0.70 mmol/L [15]. Phosphorus replacement (2.5 mg/kg) was routinely administered to patients who developed hypophosphatemia until their phosphorus levels reached the normal range.

Statistical Analysis

Data were analysed using SPSS 22.0. Continuous variables were expressed as median (25–75 quartile). Categorical variables are reported as frequencies or percentages. Differences between the two groups were assessed using the Mann Whitney U-test for continuous variable, according to normal distribution and χ^2 test for categorical variables. The Spearman's correlation coefficient was calculated to investigate the correlations between serum phosphorus levels and both CTP and MELD scores in the first seven study days in patients with and without RH. Statistical significance was set at $p<0.05$ for all tests.

RESULTS

Fifty patients with liver cirrhosis were recruited for this study. The median age of the patients was 64 years (range, 55–70 years), and 54% of them were males. The most common reason for hospital admission was investigation of the aetiology of cirrhosis (50%), followed by variceal bleeding (18%), ascites (10%), and supportive treatment (8%). The most frequent aetiology of liver cirrhosis was cryptogenic liver disease (46%); other etiologic factors are summarised in Table I. Loop diuretics were used in 14 of the 50 patients. Five patients received tenofovir therapy and three patients received entecavir therapy. In the cohort, the median initial CTP score was 6.0 (4.0–7.3), and the median initial MELD score was 10.5 (9.0–14.0). The median length of hospital stay was 15 days (range: 14-20 days). At baseline, median serum levels of (interquartile range) potassium was 4.27 (3.97–4.56) mmol/L and magnesium was 0.78 (0.73–0.85) mmol/L in the patients. Hypopotassaemia was present in only two of the patients (Table I).

Table I. Patient demographic and clinical data

	Total (n=50)
Age (years)	64.0 (55.5-70.0)
Gender, n (%)	
Male	27 (54)
Female	23 (46)
BMI (kg/m^2)	29.3 (25.6-32.8)
Reason for admission, n (%)	
Etiology examination	25 (50)
Bleeding	9 (18)
Ascites	5 (10)
Hepatocellular carcinoma	4 (8)
Support treatment	4 (8)
Hepatic encephalopathy	3 (6)
Etiology of liver cirrhosis, n (%)	
Cryptogenic liver cirrhosis	23 (46)
Hepatitis B	8 (16)
Steatohepatitis	7 (14)
Hepatitis C	6 (12)
Primary biliary cholangitis	2 (4)
Primary sclerosing cholangitis	1(2)
Portal vein thrombosis	1 (2)
Alcoholic cirrhosis	1 (2)

Table I (continued)

Use of drugs, n (%)	
Tenofovir	5 (10)
Entecavir	3 (6)
Loop diuretics	14 (28)
CTP score	6.0 (4.0-7.3)
CTP classification	
A	32 (64)
B	14 (28)
C	4 (8)
MELD score	10.5(9.0-14.0)
MELD score	
1-10 point	20
10-19 point	30
Length of hospital stay (day) (IQR)	15.0 (14.0-20.0)
SGA, n (%)	
A, well nourished	22 (44)
B, mild/moderately undernourished	19 (38)
C, severely undernourished	9 (18)
Route of nutrition, n (%)	
None	1 (2)
Regular diet+oral nutritional supplement	41 (82)
Enteral tube feeding	2 (20)
PN	4 (8)
Enteral tube feeding +PN	2 (4)
Daily energy target, kcal/day	1622.9 (1508.7-1772.9)
Baseline daily calorie intake, kcal/day	1400.0 (975.0-1625.0)
Baseline daily calorie intake, kcal/kg/day	18.8 (11.4-22.3)
Adequacy of nutritional target, %	89.2 (52.4-104.9)

BMI: body mass index; CTP: Child Turcotte Pugh; MELD: Model for End-Stage Liver Disease. *All data are presented as median (IQR).

Twelve of the 50 patients (24%) had RH during the first 14 days. These patients were then assigned to the RH group. Refeeding hypophosphatemia was more frequent on days 4 and 10 of follow-up (Fig. 1). As shown in Table II, there was no significant difference between the age and sex of patients with and without RH (p=0.312 and p=0.380), respectively.

Patients with CTP B (34%) and C (16%) scores were higher in the RH group than in the non-RH group, although there was no statistically significant (p=0.567) as shown in Fig. 2.

There was no statistically significant difference between the RH and non-RH groups in terms of nutritional status, according to the SGA score (p=0.905). However, the ratio of SGA-B and SGA-C was higher in the RH group compared to that in the non-RH group (42% vs. 37% and 42% vs. 10%) (Table III).

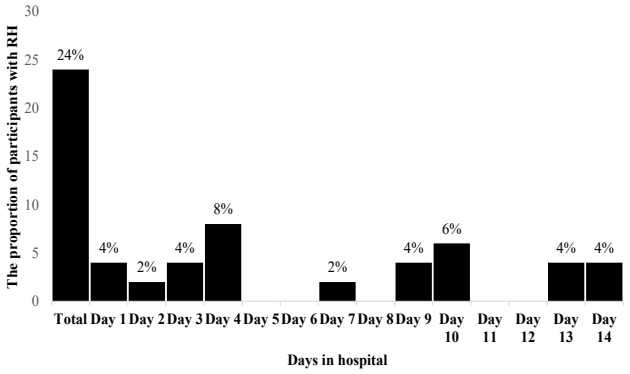

Fig. 1. Proportion of patients with RH.

Table II. Demographic and clinical data of RH and Non-RH Group

	RH (n=12)	Non-RH (n=38)	p
Age (years)	66.5 (59.0-73.0)	64.0 (54.5-69.5)	0.312
Gender, n (%)			0.380
Male	6 (50)	21 (55)	
Female	6 (50)	17 (45)	
BMI (kg/m^2)	26.1 (23.4-31.2)	29.3 (2.63-33.0)	0.612
Reason for admission, n (%)			0.467
Etiology examination	7 (58.3)	18 (47.4)	
Bleeding	2 (16.8)	7 (18.4)	
Ascites	0	5 (13.2)	
Hepatocellular carcinoma	1 (8.3)	3 (7.9)	
Support treatment	1 (8.3)	3 (7.9)	
Hepatic encephalopathy	1 (8.3)	2 (16.7)	
Etiology of liver cirrhosis, n (%)			0.441
Cryptogenic liver cirrhosis	5 (41.7)	18 (47.4)	
Hepatitis B	2 (16.7)	6 (15.8)	
Steatohepatitis	2 (16.7)	5 (13.2)	
Hepatitis C	1 (8.3)	5 (13.2)	
Primary biliary cholangitis	0	2 (5.3)	
Primary sclerosing cholangitis	1 (8.3)	0	
Portal vein thrombosis	0	1 (2.6)	
Alcoholic cirrhosis	1 (8.3)	0	
Use of drugs, n (%)			0.062
Tenofovir	2 (16.7)	3 (7.9)	
Entecavir	0	3 (7.9)	
Loop diuretics	7 (58.3)	7 (18.4)	
CTP score	6.5 (5.0-7.0)	6.0 (4.0-8.0)	0.478
CTP classification			0.567
A	6 (50)	26 (68)	
B	4 (34)	10 (26)	
C	2 (16)	2 (6)	
MELD score	11.0 (9.0-14.0)	10.0 (9.0-13.3)	0.643
MELD score			0.892
1-10 point	5 (41.7)	15 (39.5)	
10-19 point	7 (58.3)	23 (60.5)	
Length of hospital stay (day) (IQR)	16.0 (14.0-21.0)	14.0 (14.0-15.0)	0.123

For abbreviations see Table I. *All data are presented as median (IQR). p-value shows the difference between RH group and non-RH group.

According to the SGA criteria, 38% of the patients were mildly/moderately malnourished and 18% were severely malnourished. Eighty-two percent of all the patients received regular diet plus oral nutritional supplements, and 8% (four patients) received PN. Additionally, patients receiving PN (four patients, 8%) experienced significantly more RH incidence than other groups did (p<0.05). The median adequacy of the daily energy requirements in the non-RH group was similar to the RH group (91.4% vs. 89.2%, p=0.889). The targeted daily energy intake was achieved in both groups. Patients receiving regular diet plus oral nutritional supplements reached a median of 93.7% of their daily energy requirements. The median values of 75.0%, 79.6%, and 111.2% of daily energy targets were achieved by participants receiving only enteral tube feeding, PN, and enteral tube feeding plus PN, respectively (Table III).

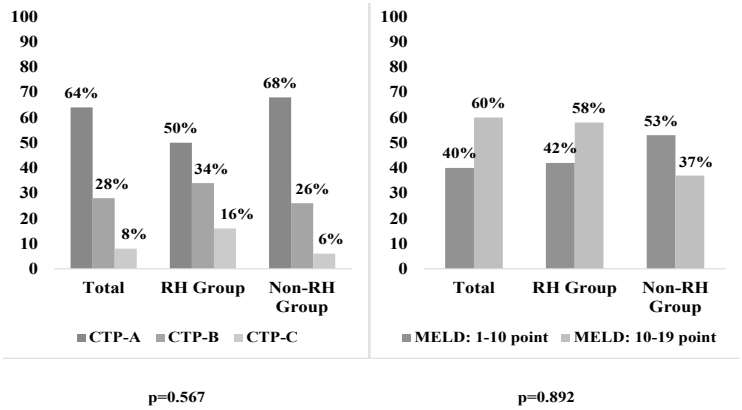

Fig. 2. The CTP and MELD scores according to RH and Non-RH Group.

Phosphate levels were within normal range in the RH [2.1–2.7 mg/dL (median: 2.5)] and non-RH [2.6–3.5 mg/dL (median: 3.0)] groups on the first day of the study. Serum phosphate levels slightly decreased during the first four days of follow-up and reached their lowest levels [1.7–2.9 mg/dL (median: 2.3)] on the fourth day in the RH group. After a phosphate replacement therapy, the RH group had the highest serum phosphate value on day eight [2.4–3.2 mg/dL (median: 3.1)]. Serum phosphate concentrations declined on day 10 of the follow-up, with a range of 2.1–3.0 mg/dL (median: 2.3). The non-RH group showed normal serum phosphate levels during hospitalisation (Fig. 3).

In the RH group, the CTP score strongly correlated negatively with serum phosphorus levels on days two (Rho = -0.805, p=0.016), three (Rho = -0.812, p=0.050), and seven (p=0.844, p=0.017). In the non-RH group, the CTP score did not correlate with serum phosphorus levels during the study period (p>0.05). There was no significant correlation between the MELD scores and serum phosphorus levels at any time point (p>0.05) (Table IV and Fig. 4). In both the groups, daily energy intake did not correlate with serum phosphorus levels during the study period (p>0.05).

DISCUSSION

Liver cirrhosis is characterised by liver parenchymal failure. Malnutrition resulting from hepatic impairment is a common clinical condition. The nutritional status of patients with liver cirrhosis is typically assessed using the SGA scoring system [16]. In our study, we evaluated the nutritional status of patients with cirrhosis and found that half of them were malnourished. These patients with liver cirrhosis diagnosis were evaluated for RH, and 24% of the patients developed RH. In our study, the RH group had worse nutritional status than the non-RH group. Additionally, two patients in the RH group were hospitalised in the intensive care unit for a long time (16 and 30 days), which has a high malnutrition risk before admission. In our study samples, 82% of the patients received oral feeding and/or enteral feeding. Refeeding hypophosphatemia developed in all the patients who were parenterally fed. Parenteral nutrition can be considered as a factor that increases the risk of RH. Similarly, a study was performed in which 48% of the patients who developed RH were fed with artificial nutrition (EN and/or PN) and reported a high risk of recurrence-free survival (RFS) compared to that of other patients [17].

Table III. Patient with RH and non-RH nutritional data

	RH (n=12)	Non-RH (n=38)	P
SGA, n (%)			0.905
A, well nourished	2 (16)	20 (53)	
B, mild/moderately undernourished	5 (42)	14 (37)	
C, severely undernourished	5 (42)	4 (10)	
Route of nutrition, n (%)			0.001
None	1 (8)	0	
Regular diet+oral nutritional supplement	5 (43)	36 (94)	
Enteral tube feeding	1 (8)	1 (3)	
PN	4 (33)	0	
Enteral tube feeding +PN	1 (8)	1 (3)	
Daily energy target, kcal/day	1563.2 (1441.5-1842.9)	1643.2 (1508.7-1772.9)	0.681
Baseline daily calorie intake, kcal/day	1200.0 (525.0-1551.0)	1402.0 (1156.0-1667.5)	0.368
Baseline daily calorie intake, kcal/kg/day	18.5 (7.7-21.4)	18.7 (13.2-22.5)	0.517
Adequacy of nutritional target, %	91.4 (43.1-105.2)	89.2 (52.4-104.9)	0.889

SGA: Subjective Global Assessment; NICE: National Institute for Health and Care Excellence; EN: enteral nutrition; PN: parenteral nutrition. All data presented as median (IQR). p-value shows the difference between RH group and non-RH group.

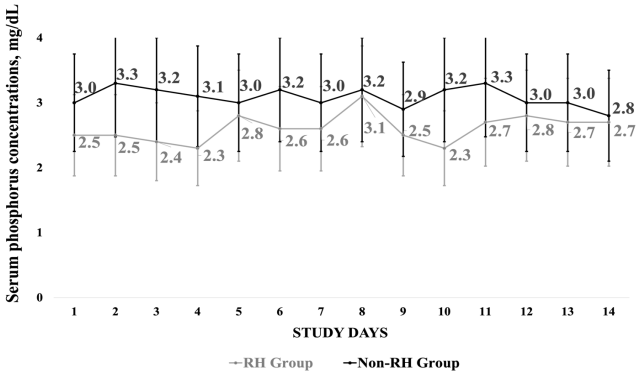

Fig. 3. Serum phosphate levels in RH and Non-RH groups during follow-up.

The risk of RFS may be greater with EN or PN than with oral intake. Therefore, artificial feeding should be initiated at a carefully reduced calorie rate [18]. This is explained by stimulated insulin secretion following intravenous administration of high glucose levels found in PN solutions, which leads to hypophosphataemia, hypokalaemia, and hypomagnesaemia [14]. The PN-fed participants in this study developed a significantly higher rate of RH than those of participants fed with other diets. However, 53% of patients in the group that did not develop RH had a good nutritional level, according to the SGA.

Nutritional indices significantly contribute to both CTP and MELD scores when assessing a patient's prognosis. A previous study has shown that malnutrition and malnutrition related to the stage of cirrhosis may lead to a high risk of developing RH in patients with cirrhosis.

These findings suggest that malnutrition status is related to cirrhosis stage, and that malnutrition may lead to a high risk of RH development in patients with cirrhosis [19].

Our results showed that the CTP score was low in patients with good nutritional status (SGA-A), and the CTP score was high in those with mild, moderate, or poor nutritional status.

We can explain why the CTP score and serum phosphorus levels were negatively correlated in patients with RH.

It was observed that the highest incidences of RH developed on days 4 (33,3%) and 10 (25%) of the 14-day follow-up of the patients. Intensive care patients have a higher disease burden and malnutrition risk than those of clinical patients with a high incidence of RH. A study by Coşkun et al. [20] reported that RH developed at least once in 52% of 117 critically ill patients, and the most common RH incidence was 28% on day two of follow-up. Additionally, it was shown that there was a significantly longer intensive care unit stay in patients who developed RH [20]. In another study, hospital stay duration in a medical inpatient group was longer than that in a refeeding syndrome group [21]. In our study, the RH group patients had a longer hospital stay, which is consistent with these data.

The median phosphorus level was the lowest on days 4 and 10. The highest rate of RH was found on day four of hospitalization. The frequency of RH was higher in patients with malnutrition and/or PN. Phosphorus deficiency is usually caused by a low phosphorus diet. Additionally, chronic diarrhoea, vomiting, alkalizing drugs that inhibit phosphorus absorption, and urinary phosphate excretion due to renal tubular dysfunction may lead to phosphorus deficiency [22]. Fourteen (28%) of our patients had diuretics, and half of these patients experienced RH. Therefore, the use of diuretics may contribute to the development of RH. Magnesium deficiency may cause a decrease in the phosphate content of skeletal muscles and an increase in urinary excretion [23]. Our results showed that magnesium levels in patients who developed RH were within the normal range.

A prospective study of patients hospitalised for decompensated cirrhosis reported that 80% of patients had cirrhosis due to alcohol use, and hypophosphatemia was observed in 34.4% [24]. Although most of the patients had CTP A compensated liver cirrhosis, 24% of patients developed RH in this study. Therefore, close follow-up is recommended for hypophosphatemia in compensated patients to avoid hypophosphatemia for liver protection.

Alcohol consumption is an important factor in the development of hypophosphatemia. Excessive alcohol consumption disrupts the concentrations of important trace elements and increases the risk of oxidative stress and alcohol-related liver diseases [25]. Acute hypophosphatemia due to phosphorus deficiency can be observed in patients hospitalised for problems related to chronic alcohol use. Approximately half of these patients develop hypophosphatemia within the first 2–3 days of hospitalization [26]. In our patient group, the

Table IV. Correlation analysis of serum phosphorus levels and CTP/MELD scores patient with RH and without RH

		RH Group (n=9)				Non-RH Group (n=41)			
		CTP		MELD		CTP		MELD	
		Rho	p	Rho	p	Rho	p	Rho	p
Serum phosphorus level	Day 1	0.458	0.254	-0.282	0.498	-0.129	0.461	-0.122	0.484
	Day 2	-0.805	0.016	-0.114	0.788	0.394	0.069	0.137	0.543
	Day 3	-0.812	0.050	-0.273	0.600	-0.125	0.511	-0.018	0.927
	Day 4	-0.012	0.977	0.319	0.441	0.092	0.670	0.249	0.240
	Day 5	-0.209	0.653	-0.262	0.571	-0.047	0.823	0.027	0.898
	Day 6	-0.551	0.257	-0.062	0.908	-0.224	0.315	-0.116	0.606
	Day 7	-0.844	0.017	-0.047	0.920	0.255	0.240	0.186	0.395

CTP: Child-Turcotte-Pugh; MELD: Model for End-Stage Liver Disease.

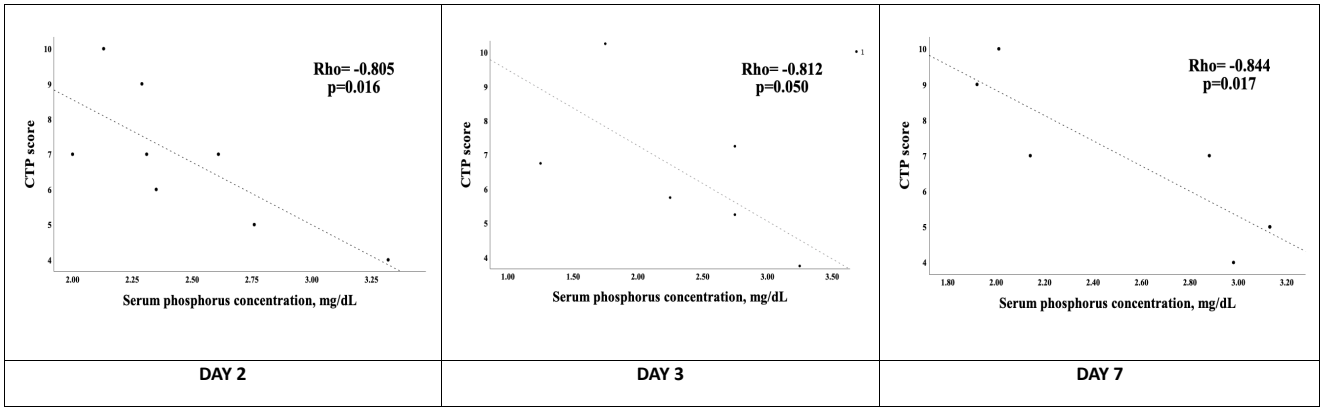

Fig. 4. The correlation between CTP score and serum phosphorus level of the RH group.

RH rate may have been lower because alcohol-related liver cirrhosis was not diagnosed. Only one patient with alcohol-related cirrhosis developed RH in our study.

Antiviral therapy is known to cause varying degrees of hypophosphatemia in patients with chronic hepatitis B. Entecavir or tenofovir should be considered for patients with hepatitis B related liver cirrhosis. Tenofovir treatment carries a potential risk of hypophosphatemia [27]. Viral hepatitis was the most frequent etiology of liver cirrhosis in our patient group. Eight patients had hepatitis B infection, five of whom received tenofovir therapy. Of these, two patients developed RH during the follow-up period. Tenofovir is involved in the aetiology of hypophosphatemia and may contribute to the development of RH. In our study, the patients who developed RH received tenofovir and/or diuretics. The risk of developing RH increases in malnourished patients with cirrhosis who use these drugs.

CONCLUSIONS

One-fourth of the patients with liver cirrhosis in this study developed RH. Our study contributes to revealing the risk of RH in patients with cirrhosis in the absence of data on the frequency of RH in these patients. This study also showed that artificial feeding carries a significant risk of RH. It should be considered that RH may develop, especially in patients fed with PN. In daily practice, we recommend the evaluation of patients with advanced-stage cirrhosis for RH.

Conflicts of interest: None to declare.

Authors' contribution: K.G and G.C.S. conceived and designed the study. G.C.S., T.O., S.T., S.S., K.G. collected and analyzed the data. K.G., A.Y., G.G. and G.C.S. interpreted the data; T.O., K.G., G.C.S., and A.Y. drafted the manuscript. All authors critically revised the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, read and approved the final manuscript.

REFERENCES

1. Nunes G, Santos CA, Barosa R, Fonseca C, Barata AT, Fonseca J. Outcome and Nutritional Assessment Of Chronic Liver Disease Patients Using Anthropometry And Subjective Global Assessment. Arq Gastroenterol 2017;54:225-231. doi:10.1590/S0004-2803.201700000-28
2. McFarlane M, Hammond C, Roper T, et al. Comparing assessment tools for detecting undernutrition in patients with liver cirrhosis. Clin Nutr ESPEN 2018;23:156–161. doi:10.1016/j.clnesp.2017.10.009
3. Maharshi S, Sharma BC, Srivastava S. Malnutrition in cirrhosis increases morbidity and mortality. J Gastroenterol Hepatol 2015;30:1507-1513. doi:10.1111/jgh.12999
4. Solomon SM, Kirby DF. The refeeding syndrome: a review. JPEN J Parenter Enteral Nutr 1990;14:90–97. doi:10.1177/014860719001400190
5. National Collaborating Centre for Acute Care (UK). Nutrition Support for Adults Oral Nutrition Support. Enteral Tube Feeding and Parenteral Nutrition. London: National Collaborating Centre for Acute Care (UK); 2006:627.
6. Marik PE, Bedigian MK. Refeeding hypophosphatemia in critically ill patients in an intensive care unit. A prospective study. Arch Surg 1996;131:1043-1047. doi:10.1001/archsurg.1996.01430220037007
7. Tresley J, Sheean PM. Refeeding syndrome: recognition is the key to prevention and management. J Am Diet Assoc 2008;108:2105-2108. doi:10.1016/j.jada.2008.09.015
8. Lai JC, Tandon P, Bernal W, et al. Malnutrition, Frailty, and Sarcopenia in Patients with Cirrhosis: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2021;74:1611-1644. doi:10.1002/hep.32049
9. Child CG, Turcotte JG. Surgery and portal hypertension. In: Child CG. The liver and portal hypertension. Philadelphia: Saunders; 1964:50-64.
10. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464–470. doi:10.1053/jhep.2001.22172
11. Duerksen DR, Laporte M, Jeejeebhoy K. Evaluation of Nutrition Status Using the Subjective Global Assessment: Malnutrition, Cachexia, and Sarcopenia. Nutr Clin Pract 2021;36:942-956. doi:10.1002/ncp.10613
12. Stephenson GR, Moretti EW, El-Moalem H, Clavien PA, Tuttle Newhall JE. Malnutrition in liver transplant patients:preoperative subjective global assessment is predictive of outcome after liver transplantation. Transplantation 2001;27:666–670. doi:10.1097/00007890-200108270-00018
13. Plauth M, Bernal W, Dasarathy S. ESPEN guideline on clinical nutrition in liver disease. Clin Nutr 2019;38:485–521. doi:10.1016/j.clnu.2018.12.022
14. Doig GS, Simpson F, Heighes PT, et al. Refeeding Syndrome Trial Investigators Group. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a

randomised, parallel-group, multicentre, single-blind controlled trial. Lancet Respir Med 2015;3:943-952. doi:10.1016/S2213-2600(15)00418-X
15. Rio A, Whelan K, Goff L, Reidlinger DP, Smeeton N. Occurrence of refeeding syndrome in adults started on artificial nutrition support: prospective cohort study. BMJ Open 2013;3:e002173. doi:10.1136/bmjopen-2012-002173
16. Zambrano DN, Xiao J, Prado CM, Gonzalez MC. Patient-Generated Subjective Global Assessment and Computed Tomography in the assessment of malnutrition and sarcopenia in patients with cirrhosis: Is there any association? Clin Nutr 2020;39:1535-1540. doi:10.1016/j.clnu.2019.06.018
17. Hernández-Aranda JC, Gallo-Chico B, Luna-Cruz ML, et al. Malnutrition and total parenteral nutrition: a cohort study to determine the incidence of refeeding syndrome. Rev Gastroenterol Mex 1997;62:260-265.
18. Reber E, Friedli N, Vasiloglou MF, Schuetz P, Stanga Z. Management of Refeeding Syndrome in Medical Inpatients. J Clin Med 2019;8:2202. doi:10.3390/jcm8122202
19. Gunsar F, Raimondo ML, Jones S, et al. Nutritional status and prognosis in cirrhotic patients. Aliment Pharmacol Ther 2006;24:563-572. doi:10.1111/j.1365-2036.2006.03003.x
20. Coşkun R, Gündoğan K, Baldane S, Güven M, Sungur M. Refeeding hypophosphatemia: a potentially fatal danger in the intensive care unit. Turk J Med Sci 2014;44:369-374. doi:10.3906/sag-1211-49
21. Friedli N, Baumann J, Hummel R, et al. Refeeding syndrome is associated with increased mortality in malnourished medical inpatients: Secondary analysis of a randomized trial. Medicine (Baltimore) 2020;99:e18506. doi:10.1097/MD.0000000000018506
22. De Marchi S, Cecchin E, Basile A, Bertotti A, Nardini R, Bartoli E. Renal tubular dysfunction in chronic alcohol abuse--effects of abstinence. N Engl J Med 1993;329:1927–1934. doi:10.1056/NEJM199312233292605
23. Knochel JP. Hypophosphatemia in the Alcoholic. Arch Intern Med 1980;140:613-615. doi:10.1001/archinte.1980.00330170029018
24. Llibre-Nieto G, Lira A, Vergara M, et al. Micronutrient Deficiencies in Patients with Decompensated Liver Cirrhosis. Nutrients 2021;13:1249. doi:10.3390/nu13041249
25. Baj J, Flieger W, Teresiński G, et al. Magnesium, Calcium, Potassium, Sodium, Phosphorus, Selenium, Zinc, and Chromium Levels in Alcohol Use Disorder: A Review. J Clin Med 2020;9:1901. doi:10.3390/jcm9061901
26. Elisaf MS, Siamopoulos KC. Mechanisms of hypophosphataemia in alcoholic patients. Int J Clin Pract 1997;51:501–503.
27. Lee D, Yun BC, Seo KI, et al. Risk factors associated with hypophosphatemia in chronic Hepatitis B patients treated with tenofovir disoproxil fumarate. Medicine (Baltimore) 2019;98:e18351. doi:10.1097/MD.0000000000018351