Original Paper

Calcium and Phosphorus Deficiencies in Patients with Liver Cirrhosis

CLAUDIU MARINEL IONELE[1], MIHAELA SIMONA SUBTIRELU[2], BOGDAN SILVIU UNGUREANU[3], MIRCEA-SEBASTIAN SERBANESCU[4], ION ROGOVEANU[3]

[1]*Ph.D. student, Doctoral School, University of Medicine and Pharmacology of Craiova, Romania*

[2]*Department of Pharmacoeconomics, University of Medicine and Pharmacy of Craiova, Romania*

[3]*Department of Gastroenterology, University of Medicine and Pharmacy of Craiova, Romania*

[4]*Department of Medical Informatics, University of Medicine and Pharmacology of Craiova, Romania*

ABSTRACT: Patients with cirrhosis often develop malnutrition and micronutrient deficiencies, leading to a worse prognosis and increased mortality. Our purpose was to assess the prevalence of micronutrient deficiencies especially calcium and phosphorus in patients with decompensated liver cirrhosis (LC). This was a retrospective study including 143 consecutive patients hospitalized for acute decompensation of cirrhosis, most of them with alcoholic etiology along with viral B or viral C and autoimmune induced cirrhosis. A blood test including minerals was performed on admission. Lower serum calcium levels were found in patients with a more severe forms of LC and also the ones diagnosed with viral and alcoholic LC rather than autoimmune induced LC. Peritoneal ascitic fluid was observed in 51 patients with hypocalcemia and only 24 patients with normal calcium levels had fluid accumulation. Low levels of phosphorus were noted in patients with a more severe form of LC (chi-square: 20.2504; p-value 0.000446). Ascitic fluid was found in patients with low values of phosphorus as well as in those with hypocalcemia (chi-square 5.235; p-value 0.022137). In conclusion, this study confirmed that patients with advanced liver disease had lower values of calcium and phosphorus and a more severe form of LC can be associated with hypocalcemia and hypophosphatemia.

KEYWORDS: *Liver cirrhosis, calcium, phosphorus.*

Introduction

Liver cirrhosis (LC) is the end-stage of many different chronic liver diseases, characterized by architectural distortion and hepatic with the formation of regenerative nodules and has varied clinical manifestations and complications [1].

The main causes of LC are alcoholic liver disease (ALD), hepatitis B (HBV), hepatitis C (HCV), and autoimmune liver disease such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) [2,4].

The liver regulates the metabolic pathways, is involved in the transport of trace elements and consequently ensures their bioavailability and tissue distribution.

It also plays a role in the excretion of trace elements through bile formation. [5].

Calcium is the fifth most abundant element in the body, it is essential in skeletal mineralization, as well as a wide range of biologic functions, it has a structural role in cell membrane function and intracellular signaling.

Calcium is only available to the body through dietary sources [6].

Phosphorus is an essential mineral which plays multiple roles in the body [7].

It is a key element of bones and most of the uptake occurs in the liver and the skeletal muscle [7].

There are three major mechanisms by which hypophosphatemia can occur: decreased intestinal absorption, internal redistribution, and increased urinary loss [8].

There is often a combination of factors responsible for hypophosphatemia.

The following factors are potentially involved in the alcoholic patient: a poor dietary intake of phosphate and vitamin D, chronic diarrhea, increased urinary loss due to secondary hyperparathyroidism induced by vitamin D deficiency and a direct toxic effect of alcohol on the proximal tubule [8-10].

Malnutrition is a common complication in patients with LC and after a thorough research, several studies have shown its association with increased morbidity and mortality and decreased quality of life [5].

If for zinc and iron it is customary to find deficiencies, when it comes to levels of minerals such as calcium, magnesium and phosphorus in the serum of cirrhotic patients, there are not many available studies [11,14].

Patients with advanced liver disease have an increased risk of micronutrient deficiencies that

10.12865/CHSJ.48.03.09

arise from anorexia, diuretic use, fat malabsorption, and hepatitis C.

Because patients with ascites have restricted intake of animal protein and are taking diuretics, they commonly acquire zinc deficiency [15].

Similarly, magnesium deficiency can result from decreased oral intake of nutrients and use of diuretics [15,16].

The most recent guideline published in 2018 by the European Association for the Study of the Liver (EASL) on nutrition recognized that for patients with chronic liver disease there are no specific studies or evidence on the benefit of micronutrient supplementation in patients with cirrhosis.

However, they suggested that confirmed deficiencies should be supplemented in accordance with the general recommendations for usual clinical practice [17].

The majority of studies evaluating the prevalence of micronutrient deficiencies in decompensated LC have a small number of subjects and there were assessed only certain micronutrients [18,19].

The aim of this study was to determine the prevalence of micronutrient deficiencies in patients with LC of any etiology and any degree of liver failure and which of these deficiencies are correlated with the severity of liver disease.

Materials and Methods

Study Design and Patients

In this retrospective study we included patients confirmed with LC due to alcohol use, viral B and viral C cirrhosis and patients diagnosed with primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC).

All the patients included in our study were admitted in the hospital due to hepatic decompensation (hepatic encephalopathy, ascites or portal hypertensive bleeding) or for routine checkup of patients with anterior decompensation.

Newly or previously diagnosed patients with LC hospitalized in the Gastroenterology department of the County Clinical Emergency Hospital of Craiova, Romania were included.

The period of admission was set between January 2019 and December 2020, during pandemics, and we collected their data using existing records from the clinic.

The exclusion criteria from the study were: patients who were under treatment with calcium, magnesium or phosphorus supplements.

Also, we did not take into consideration for this study patients diagnosed with hepatocellular carcinoma or other malignancies, kidney failure and documented bone disease like osteopenia and osteoporosis.

The current study protocol strictly adhered to all regulations of the Declaration of Helsinki and it was approved by the ethics committee of the University of Medicine and Pharmacy of Craiova, Romania (No. 173/29.10.2021)

Biological Analyses

The Model for End-stage Liver Disease (MELD) and Child-Pugh scores were used to assess the prognosis of patients.

MELD score was determined for all the patients and is based on total bilirubin, creatinine and international normalized ratio (INR).

In a systematic review of 118 studies outlining the prognostic of survival in cirrhosis, MELD score was underlined as predictor of long-term survival rate in patients with decompensated LC [20,21].

The Child-Pugh scoring system was also assessed for all patients.

It is a score designed to predict mortality in cirrhosis patients and to guide the selection of those patients who would benefit from elective surgery for portal decompression.

It has 6 clinical and laboratory criteria to categorize patients: presence of peritoneal fluid, hepatic encephalopathy, nutritional status, total bilirubin, albumin and INR.

All the patients were divided by Child-Pugh classification into three categories: A-good hepatic function, from 5 to 6 points, B-moderately impaired hepatic function, 7 from to 9 points and C-advanced hepatic dysfunction from 10 to 15 points in which a higher score indicates more severe liver dysfunction [22,24].

All the patients had upper endoscopy, blood samples taken for measuring aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (yGT), magnesium, phosphorus, calcium, alkaline phosphatase, platelet count, hemoglobin, creatinine, total bilirubin, all of them being determined by automated routine procedures.

We also recorded the presence of hepatic complications like ascitic decompensation, spontaneous bacterial peritonitis, hepatic encephalopathy, alcoholic hepatitis and portal hypertensive bleeding.

In addition, micronutrient deficiencies were defined according to the hospital laboratory reference values and considered a deficiency to be any value below the lower limit of normality.

 10.12865/CHSJ.48.03.09

Data Analysis

Patient data was logged in an Excel (Microsoft, USA) file.

Data analysis was done in part in Excel, and in part in MATLAB (MathWorks, USA).

The descriptive statistics (together with the charts) was assessed using Excel, while the inferential statistics using MATLAB.

For categorical data, we used pivot tables and the Chi-square test for statistical assessment.

Numerical data correlation was assessed using Pearson's correlation coefficient (r), considering values between 0-0.2 as non-existing correlation, 0.2-0.4 weak correlation, 0.4-0.6 reasonable correlation, 0.6-0.8 high correlation, and above 0.8 very high correlation.

P-values of 0.05 or lower were considered statistically significant. Numerical variables are expressed in terms of mean and standard deviation (SD).

Results

Patients Characteristics

A total of 143 consecutive patients with proven diagnosis of LC were, we had 88 patients with alcohol induced LC, 43 patients with viral induced LC of which 30 patients had a C virus infection, 10 of them had a B virus infection and the other 3 patients had B and C virus coinfection.

Also, 12 of these patients had autoimmune induced LC patients of which 8 had PBC and the 4 other patients had PSC.

The average age of the entire group was 58.41 years±10.91 SD, the alcoholic induced cirrhosis group had an average age of 57.35 years±10.22 SD, the LC due to viral hepatitis patients had an average age of 62.70 years±10.61 SD and autoimmune LC patients had an average age of 50.83 years±11.74 SD (Tables 1,2).

Table 1. Patient's characteristics.

Variable	Value
Age	58.41±10.91
Sex	
Male	120 (83.92%)
Female	23 (16.08%)
Nutrition	
Underweight (<18.5)	4 (2.8%)
Normal weight (18.5-24.9)	68 (47.55%)
Overweight (25-26.9)	47 (32.87)
Obese (30-39.9)	22 (15.38)
Etiology of cirrhosis	
Alcohol	88 (61.15%)
Hepatitis B	10 (6.99%)
Hepatitis C	30 (20.98%)
Hepatitis B+C	3 (2.1%)
Autoimmune	12 (8.39%)
MELD	16.39±6.24
Child-Pugh class	
A	40 (27.97%)
B	61 (42.66%)
C	41 (28.67%)
Decompensation of cirrhosis	
Esophageal varices	106 (74.13%)
Encephalopathy	24 (16.78%)
Ascites	76 (53.15%)

Data are expressed in mean±SD for quantitative variables and n (%) for qualitative variables. MELD: Model for end-stage liver disease.

Table 2. Values from biologic analysis.

Parameter	Value	Reference value
AST	152.87±259.51	5-34U/L
ALT	113.38±287.01	3-55U/L
yGT	163.25±205.52	8-60U/L
Phosphatase	119.86±82.33	40-150U/L
Albumin	3.25±0.67	3.5-5.2U/L
Calcium	8.18±0.73	8.4-10.2mg/dL
Phosphorus	2.85±0.70	2.5-4.5mg/dL
Magnesium	1.79±0.44	1.6-2.6mg/dL
Hemoglobin	10.96±2.44 10.2±2.16	Male 12.6-17.4g/dL Female 11.7-16.1g/dL
Thrombocytes	139.70±220.40	150-400x10^{x3}/mm^3
Total bilirubin	2.46±2.36	0.2-1.2mg/dL
Creatinine	0.95±0.56	0.70-1.20mg/dL

Data are expressed in mean±SD or median (range); aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (yGT).

Regarding calcium values, we observed lower result in patients with a more severe form of LC assessed by Child-Pugh classification (the chi-square statistic is 14.9335. The p-value is .000572. The result is significant at $p<05$).

From Figure 1 we concluded that patients with moderately impaired hepatic function and advanced hepatic dysfunction had lower values of calcium in contrast with patients with good hepatic status.

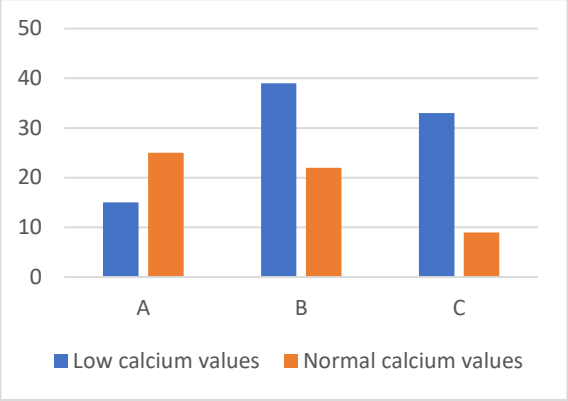

Figure 1. Calcium levels in patients divided by Child-Pugh classification.

Lower values were noted in patients diagnosed with viral and alcoholic induced LC than autoimmune caused LC (chi-square 3.2015, p-value 0.073572, but the result was not significant at $p<0.05$ (Figure 2).

From the total of 143 patients, we found that 80 of them with low calcium levels had an anterior decompensation of LC and only 42 newly diagnosed patients had normal calcium levels (the chi-square statistic is 7.8165. with a p-value of 0.005177 (Figure 3).

The result is significant at $p<0.05$).

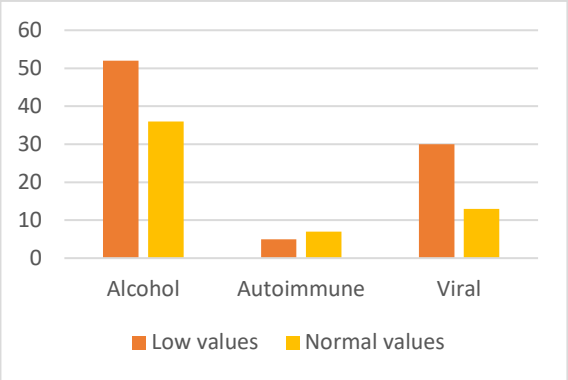

Figure 2. Calcium levels in different etiologies of liver cirrhosis.

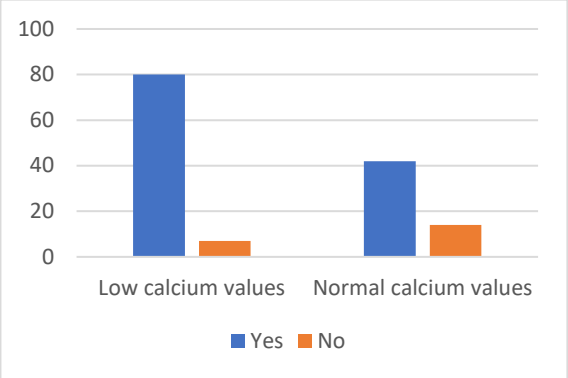

Figure 3. Lower calcium values were observed in patients with anterior decompensation.

Low levels of phosphorus were observed in patients with a more severe form of LC (chi-square: 20.2504; p-value 0.000446) but there were no significant differences between etiologies (chi-square: 1.3389, p-value 0.512) (Figures 4-5).

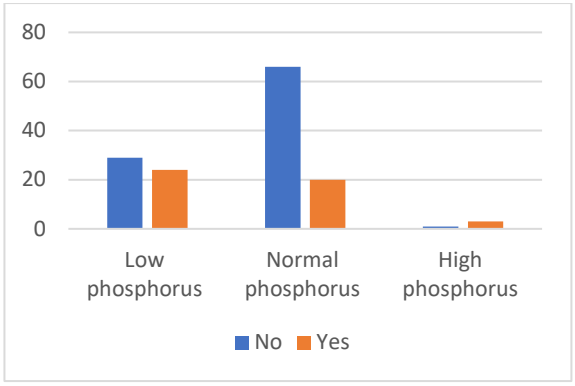

Figure 4. Presence of jaundice.

Also, ascites, as mark of LC decompensation was diagnosed in patients with low values of phosphorus (chi-square 5.235; p-value 0.022137) (Figure 6).

As calcium in Figure 1, phosphorus was lower in patients with a more severe form of cirrhosis.

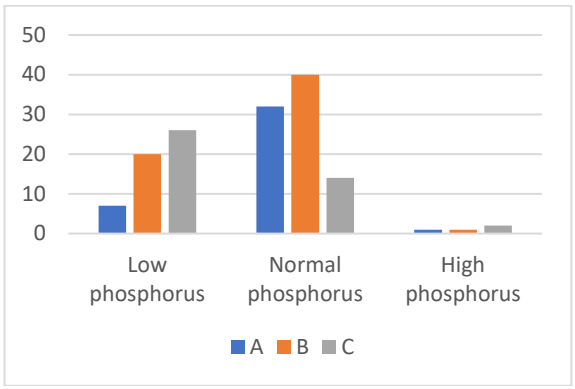

Figure 5. Phosphorus levels in patients divided by Child-Pugh classification.

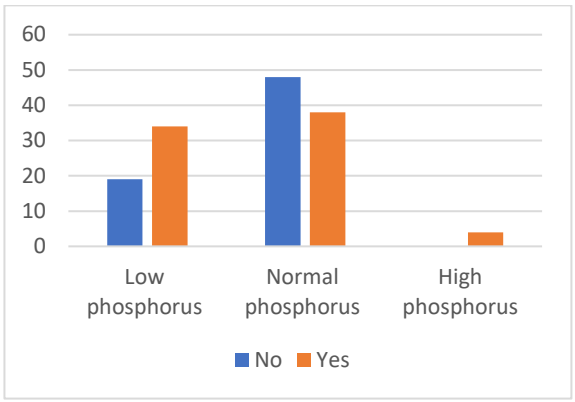

Figure 6. Phosphorus values in patient with and without peritoneal ascites.

10.12865/CHSJ.48.03.09

Discussion

Minerals play a significant role in anti-inflammatory and anti-apoptotic metabolic processes, and their impairment are common in patients with liver cirrhosis regardless of the etiology of liver disease.

Our study aims to provide an overall view of calcium and phosphorus levels in patients with LC due to alcohol consumption, viral B and viral C induced LC or autoimmune etiology (PBC and PSC).

To date, the most documented deficiency in cirrhotic patients is the lack of calcium.

According to the literature, calcium was normal in most of the patients found in other study; also, calcium supplementation in elderly subjects with a high prevalence of hypocalcemia normalized serum markers of calcium after 1 year of treatment [25].

In our study, the prevalence of calcium deficiency was higher in viral and alcoholic induced LC than autoimmune caused LC.

Lower values of calcium were observed in patients with a more severe form of LC assessed by Child-Pugh classification.

It is well-known that patients with liver disease develop bone loss that can lead to atraumatic fractures Nakchbandi et al. recommended that physicians should evaluate bone density in cirrhotic patients regardless of serum calcium values and also, they should supplement with a minimum of vitamin D and calcium to prevent bone fractures and osteoporosis [26].

We observed in our patients a strong correlation between severity of cirrhosis expressed by Child Pugh classification, the majority of hypocalcaemic patients were diagnosed with advanced LC.

Also, there is a strong correlation between low levels of calcium and albumin deficiency in patients with advanced liver disease [27].

In relation to minerals, the prevalence of phosphorous deficiency was also high and we observed correlation between low levels of phosphorus and decreased levels of calcium. Hypophosphatemia has been reported in the setting of hepatic failure (HF) [28,29].

Patients with cholestatic liver disease have poor absorption of both fat and fat-soluble vitamins including vitamin D.

Low vitamin D levels can lead to secondary hyperparathyroidism and it functions by stimulating intestinal calcium and phosphorus absorption, by increasing bone calcium mobilization, and by increasing renal reabsorption of calcium in the distal tubule [30].

Phosphorus repletion towards normal levels led to clinical improvement in this case, and the authors hypothesized that hypophosphatemia may have been the cause of acute hepatocellular necrosis [31].

A statistically significant better prognosis was observed in patients with normal phosphorus levels in the study presented by Baquerizo et al. [32].

It is known that patients with decompensated LC are taking diuretics and Dohyeong et al. suggested that liver function can influence the incidence of hypophosphatemia; the risk of hypophosphatemia in patients with cirrhosis is about 3.4-fold greater than in patients with normal liver function [33].

Conclusion

We can say that a low phosphorus level together with other prognostic factors such as total serum bilirubin, degree of encephalopathy can help guide decisions regarding the best treatment for liver cirrhosis.

We noticed in our study that for patients with advanced liver disease, lower values of calcium and phosphorus were recorded.

Moreover, the more advanced the liver disease can lead to a greater the risk of hypophosphatemia and hypocalcemia.

There should also be more attention on assessing osteoporosis in cirrhotic patients, when diagnosing with LC or during follow-up.

Therefore, our general advice would be the dosage of calcium and phosphorus values, for which currently it is not normally done for cirrhotic patients.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. J Hepatol, 2019, 70(1):151-171.
2. Gunnarsdóttir SA. Liver cirrhosis: epidemiological and clinical aspects. In: Gunnarsdóttir SA (Eds): The Sahlgrenska Academy, Göteborg University, 2008, Göteborg, 37-40.
3. Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021, Viral hepatitis [online]. Available at: https://www.who.int/publications/i/item/9789240027077 [Accessed 05.11.2022].

4. Ionele CM, Turcu-Stiolica A, Subtirelu MS, Ungureanu BS, Cioroianu GO, Rogoveanu I. A Systematic Review and Meta-Analysis on Metabolic Bone Disease in Patients with Primary Sclerosing Cholangitis. J Clin Med, 2022, 11(13):e3807.
5. Kolachi NF, Kazi TG, Afridi HI, Kazi NG, Khan S. Investigation of essential trace and toxic elements in biological samples (blood, serum and scalp hair) of liver cirrhotic/cancer female patients before and after mineral supplementation. Clin Nutr, 2012, 31(6):967-973.
6. Iuliano S, Poon S, Robbins J, Bui M, Wang X, deGroot L. Effect of dietary sources of calcium and protein on hip fractures and falls in older adults in residential care: Cluster randomised controlled trial. BMJ, 2021, 375:n2364.
7. Kuehn K, Hahn A, Seefried L. Mineral Intake and Clinical Symptoms in Adult Patients with Hypophosphatasia. J Clin Endo Metab, 2020, 105(8):e2982-e2992.
8. Gaasbeek A, Meinders AE. Hypophosphatemia: An update on its etiology and treatment. Am J Med, 2005, 118(10):1094-1101.
9. Ryback RS, Eckardt MJ, Pautler CP. Clinical relationships between serum phosphorus and other blood chemistry values in alcoholics. Arch Intern Med, 1980, 140(5):673-677.
10. Cheung K, Lee SS, Raman M. Prevalence and Mechanisms of Malnutrition in Patients with Advanced Liver Disease, and Nutrition Management Strategies. Vol. 10, Clin Gastroenterol Hepatol, 2012, 10(2):117-125.
11. Ishizu Y, Ishigami M, Honda T, Imai N, Ito T, Yamamoto K. Decreased appetite is associated with the presence of sarcopenia in patients with cirrhosis. Nutrition, 2022, 103-104:111807.
12. Aby ES, Saab S. Frailty, Sarcopenia, and Malnutrition in Cirrhotic Patients. Clin Liver Dis, 2019, 23(4):589-605.
13. Campillo B, Richardet JP, Scherman E, Bories PN. Evaluation of nutritional practice in hospitalized cirrhotic patients: Results of a prospective study. Nutrition, 2003, 19(6):515-521.
14. Gammoh NZ, Rink L. Zinc in infection and inflammation. Vol. 9, Nutrients, 2017, 9(6):624.
15. Yoshida Y, Higashiac T, Nouso K, Nakatsukasa H, Nakamura S, Watanabe A. Effects of Zinc Deficiency in Liver Cirrhosis. Acta Med Okayama, 2001, 55(6):349-355.
16. Cheung K, Lee SS, Raman M. Prevalence and Mechanisms of Malnutrition in Patients with Advanced Liver Disease, and Nutrition Management Strategies. Vol. 10, Clin Gastroenterol Hepatol, 2012, 10(2):117-125.
17. Merli M, Berzigotti A, Zelber-Sagi S, Dasarathy S, Montagnese S, Genton L. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. J Hepatol, 2019,70(1):172-193.
18. Koop AH, Mousa OY, Pham LE, Corral-Hurtado JE, Pungpapong S, Keaveny AP. An argument for vitamin d, a, and zinc monitoring in cirrhosis. Ann Hepatol, 2018, 17(6):920-932.
19. Llibre-Nieto G, Lira A, Vergara M, Solé C, Casas M, Puig-Diví V. Micronutrient deficiencies in patients with decompensated liver cirrhosis. Nutrients, 2021, 13(4):1249.
20. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 118 studies. Vol. 44, J Hepatol, 2006, 44(1):217-231.
21. Kamath PS, Kim WR. The Model for End-stage Liver Disease (MELD). Vol. 45, Hepatology, 2007, 45(3):797-805.
22. Akarapatima K, Chang A, Prateepchaiboon T, Pungpipattrakul N, Songjamrat A, Pakdeejit S, Rattanasupar A, Piratvisuth T. Predictive Outcomes Using Child-Turcotte-Pugh and Albumin-Bilirubin Scores in Patients with Hepatocellular Carcinoma Undergoing Transarterial Chemoembolization. J Gastrointest Cancer, 2021, 53(4):1-8.
23. Lee DH, Son JH, Kim TW. New scoring systems for severity outcome of liver cirrhosis and hepatocellular carcinoma: current issues concerning the Child-Turcotte-Pugh score and the Model of End-Stage Liver Disease (MELD) score. Taehan Kan Hakhoe Chi, 2003, 9(3):167-179.
24. Tsoris A, Marlar CA. Use of The Child Pugh Score. In: Tsoris A, Marlar CA (Eds): Liver Disease, StatPearls Publishing, 2022, Treasure Island, 1-3.
25. Glatzle J, Piert M, Meile T, Besenthal I, Schäfer JF, Königsrainer A, Zittel TT. Prevalence of vertebral alterations and the effects of calcium and vitamin D supplementation on calcium metabolism and bone mineral density after gastrectomy. British Journal of Surgery, 2005, 92(5):579-585.
26. Nakchbandi IA. Osteoporosis and fractures in liver disease: Relevance, pathogenesis and therapeutic implications. Vol. 20, World J Gastroenterol, 2014, 20(28):9427-9438.
27. Jagdish RK, Maras JS, Sarin SK. Albumin in Advanced Liver Diseases: The Good and Bad of a Drug! Vol. 74, Hepatology, 2021, 74(5):2848-2862.
28. Dawson DJ, Babbs C, Warnes TW, Neary RH. Hypophosphataemia in acute liver failure. Br Med J, 1987, 295:1312-1313.
29. Moutzouri E, Liberopoulos EN, Elisaf M. Life-threatening hypophosphataemia in a cirrhotic patient with jaundice. Arch Med Sci, 2011, 7(4):736-739
30. Çaykara B, Öztürk G, Mutlu HH, Arslan E. Relationship Between Vitamin D, Calcium, and Phosphorus Levels. J Acad Res Med, 2020, 10(3):252-257.
31. Chung PY, Sitrin MD, Te HS. Serum phosphorus levels predict clinical outcome in fulminant hepatic failure. Liver Transpl, 2003, 9(3):248-253.
32. Baquerizo A, Anselmo D, Shackleton C, Chen Twei, Cao C, Weaver M, Gornbein J, Geevarghese S, Nissen N, Farmer D. Demetriou A, Busuttil RW. Phosphorus as an early predictive factor in patients with acute liver failure. Transplantation, 2003, 75(12):2007-2014.
33. Lee D, Yun BC, Seo K il, Han BH, Lee SU, Park ET, Lee JW, Jeong J. Risk factors associated with hypophosphatemia in chronic Hepatitis B patients treated with tenofovir disoproxil fumarate. Medicine, 2019, 98(50):e18351.

Corresponding Authors: Mircea-Sebastian Serbanescu, Department of Medical Informatics, University of Medicine and Pharmacology of Craiova, Romania, e-mail: mircea_serbanescu@yahoo.com