Original Article

Hepatic Encephalopathy in HCV-related Liver Cirrhosis and Serum 25-Hydroxy Vitamin D (25-OHD) in Elderly.

Marwa Ahmed Mohamed Saad [a], Nany Hassan Elgyar [a], Ali Mahmoud Ali Ramadan [a*], Mona Moustafa Tahoun [b], Yasmin Ali Ismail Ali Dkos [a]

[a] *Department of Internal Medicine, Faculty of Medicine, University of Alexandria, Alexandria, Egypt.*
[b] *Department of Clinical and Chemical Pathology, Faculty of Medicine, University of Alexandria, Alexandria, Egypt.*

Abstract

Background: Cirrhosis is the most advanced form of chronic liver disease. During the transition from the compensation phase to the decompensation period, numerous complications and a substantial decrease in life expectancy occur. Cirrhosis is mostly brought on by HCV infection 93% of the time in the world. Chronic hepatitis C was found to be much more common in those over 65, and 14% of the elderly developed liver cirrhosis. Hepatic encephalopathy (HE), a disorder of the brain brought on by underlying liver disease and portal hypertension, is an important decompensating process in cirrhosis of the liver. A recent study showed a shortage of 25-hydroxyvitamin D (25-OHD) as one of the risk factors for the development of HE.

Objective: The present research is focused on investigating the relationship between serum levels of 25-hydroxyvitamin D (25-OHD) and hepatic encephalopathy (HE) in individuals with liver cirrhosis due to HCV.

Subjects and methods: Eighty patients with liver cirrhosis brought on by HCV and aged 65 or older participated in the study. They were split into two groups: Group 1:Cirrhotic patients due to HCV including HE. Group 2:Cirrhotic patients due to HCV but no HE is included. Serum 25-OH vitamin D levels in both groups were evaluated.

Results: Vitamin D among group I varied from 3.0 – 42.0 with S.D of 10.68±7.43.vitamin-D among group II varied from 3.0 – 75.0 with S.D 13.03±10.85. Despite there being a S.D. difference, the data indicated a lack of statistical significance among the two research groups.

Conclusion: Between group I (cases) and group II (control), the serum level of 25-OH vitamin D did not differ statistically remarkably.

Keywords: Cirrhosis, hepatic encephalopathy (HE), 25-OH vitamin D

Introduction

An elderly person is over 60 years old, according to the United Nations. As people are living longer and getting older globally, the elderly are now a growing segment of the population. The globe Health Organization (WHO) estimates that there were 703 million older individuals in the globe in 2019 and that there will be 1.5 billion by 2050. [1]

Egypt is undergoing a population structural change as the number of people 60 and over is projected to greater than double coming from 8.4 million to 22 million across 2020 and 2050, accounting for 14% of the country's overall population. [2]

Given that it contributes to the evolution of liver illnesses, aging is regarded as a risk factor that couldn't be avoided. As the first signs of HCV infection, people older than 60 years and more frequently present with numerous consequences such as cirrhosis and HCC. HCV is linked to a quicker progression to fibrosis, cirrhosis, and infectious consequences at the time of first infection in older age. [3-5]

Cirrhosis is the most advanced form of chronic liver disease. During the transition from the compensation phase to the decompensation period, numerous complications and a substantial decrease in life expectancy occur. [6]

Cirrhosis is defined as long-term liver damage leading to scarring of liver tissue that impairs normal liver function. Cirrhosis can result in severe, sometimes fatal complications such as encephalopathy, hemorrhage, or liver failure. [7] Cirrhosis is mostly brought on by HCV infection 93% of the time in the world. [8] Chronic hepatitis C was found to be much more common in those over 65, and 14% of the elderly developed liver cirrhosis. [5]

Various HCV prevalence in Egypt were recorded. In the age range (15-59 years), the prevalence of HCV decreased from 14.7% in 2008 to 10% in 2015. [9] Numerous conditions, including steatohepatitis, sclerosing cholangitis, autoimmune hepatitis, and Wilson's disease, can also result in cirrhosis in addition to viral hepatitis. Additionally, alcohol can lead to cirrhosis on its own and aggravate chronic liver disease brought on by other conditions. Hepatic encephalopathy (HE), a disorder of the brain brought on by underlying liver disease and portal hypertension, is an important decompensating process in cirrhosis of the liver. [10-13]

The pathophysiology and etiology of HE is complex and multifaceted., and they include altered levels of manganese and zinc as well as impaired ammonia metabolism, dysbiosis that results in hepatic and gut inflammation, low concentrations of circulating branched amino acids, and inappropriate amounts of electrolytes. [14] Patients who experience recurrent bouts of HE typically has cumulative, long-lasting memory and learning losses. [15] Several conditions, such as spontaneous bacterial peritonitis, electrolyte imbalance, and upper gastrointestinal hemorrhage, are linked to the presentation of hepatic encephalopathy. [16] The lack of 25-hydroxyvitamin D is one of the many factors that have lately been linked to hepatic encephalopathy. [17]

The metabolism and absorption of calcium, phosphate, and magnesium are controlled by the group of fat-soluble Secosteroids known as 25-hydroxyvitamin D (25-OHD). It is also linked to numerous additional biological activities, including work as a possible immunomodulator and anti-inflammatory. [18] It has been shown that 25-OHD is linked to several neurological conditions, including Alzheimer's disease, dementia, and impaired memory. [19,20] Lack of 25-OHD is linked to several psychiatric disorders. By using stepwise linear regression and Pearson's correlation, Research has shown this low 25-hydroxyvitamin D concentrations were linked to a greater chance of dementia in both older and younger persons. [21]

Vitamin D is included in several foods and can also be produced when exposed to ultraviolet light. For vitamin D to be in its functional state, it must first go through hydroxylation in the liver, where it becomes the metabolite 25-OHD, which is the main metabolically active of vitamin D form in circulation. it’s half-life is 15 to 21 days, the 25-OHD metabolite circulates attached to the vitamin D-binding protein (DBP). The second stage involves the activation of 1,25 dihydroxy vitamin D, which primarily takes place inside the kidney. Fewer of the second steps are also present in the brain, tissues from the placenta, bone, mammary gland, monocytes, and parathyroid gland. [22]

The metabolite that is active in vitamin D is 1,25 dihydroxyvitamin D. It only has a half-life of 10 to 20 hours. For this brief half-life, the blood level of circulating 25-OHD is frequently used to determine the vitamin D level. [22] Vitamin D is regarded as

an anti-infective agent and a regulator of the immune system. Due to more severe liver illness, 25-OHD levels are declining as vitamin D is first hydroxylated in the liver into 25-OHD [23]. It is known that 92% of people with chronic liver disease (CLD) have low vitamin D levels, with at least one-third of them having a serious 25-OHD deficiency. [24,25]
A recent study showed a shortage of 25-hydroxyvitamin D (25-OHD) as one of the risk factors for the development of HE. Additionally, it's been noticed that cirrhotic individuals with decreased levels of 25-OHD have higher overall mortality. [26]
The present research is focused on investigating the relationship between serum levels of 25-hydroxyvitamin D (25-OHD) and hepatic encephalopathy (HE) in individuals with liver cirrhosis due to HCV.

SUBJECTS

The Geriatric Department, ICU units, and Outpatient Clinics of the Main University Hospital of Alexandria were used for the study. 80 participants with liver cirrhosis due to HCV were included in the research if they were sixty-five years or older. Participants were separated into :

• Group 1: 40 cirrhotic patients due to HCV including HE.
• Group 2: 40 cirrhotic patients due to HCV but no HE is included.

Exclusion criteria:

- Liver cirrhosis unrelated to HCV infection is an exclusion criterion.
- A recent two-month history of taking vitamin D.
- A history of taking a number of drugs, such as antifungal, anticonvulsant, or glucocorticoid medications, which might lower vitamin D levels.
- An earlier history of vitamin D inadequacy was brought on by conditions such as CKD, IBD, malabsorption syndrome, lymphomas, or hyperparathyroidism.

METHODS

The following methods were used on each patient:

1. A thorough history is taken, paying particular attention to information on:
- Age, occupation, sex, marital status, and unusual behaviors.
- The presence of HCV and liver cirrhosis.
- Signs of a decompensated liver (ascites, lower limb oedema, jaundice,

hematemesis, melena, And signs of HE.)
- The presence of additional comorbidities.

2. Complete clinical evaluation.
3. Laboratory examinations, such as

- Routine Laboratory Examinations:
  - CBC, or complete blood count.
  - Blood urea and creatinine levels tests for kidney function.
  - Total bilirubin, serum albumin, AST, and ALT tests for liver function.
  - Sodium and potassium
  - PTT, PT, and INR for assessing coagulation profile.
- Virology evaluation: HBsAg and HCV antibodies.
- Evaluation of serum 25-OH vitamin D levels.

4. Radiological examinations: Abdominal and pelvic ultrasound for detection of liver cirrhosis.
5. The West Haven criteria are used to determine the severity of patients who have HE.
   West Haven criteria divide clinically evident HE into four grades. Patients in grade I have a lack of concentration and some mild personality changes that are mostly visible to their families. The most noteworthy observation in grade II is confusion about time mixed with improper behavior and tiredness. Patients in grade III are stuporous but responsive to stimuli. They may also behave strangely and appear to be disoriented to place and time. Patients in grade IV are in coma. [27]
6. A determination of the disease's severity utilizing the Model for End-Stage Liver Disease (MELD) and Child Turcotte Pugh (CTP) scores. MELD score is calculated using serum bilirubin, serum creatinine, and International Normalized Ratio (INR) and is given by the formula $9.57 \times \log_e(\text{creatinine}) + 3.78 \times \log_e(\text{total bilirubin}) + 11.2 \times \log_e(\text{INR}) + 6.43$. Patients are given a score between 6 and 40 based on the MELD score, corresponding to an anticipated 3-month survival rate between 90% and 7%, respectively. Patients are considered candidates for liver transplantation if they

have a MELD score of 17 or more. [28]

The child-Turcotte-Pugh score was created to predict mortality in cirrhotic patients. it divides patients into three categories: A - good hepatic function, B - moderately impaired hepatic function, and C - advanced hepatic dysfunction. Five clinical and laboratory criteria were employed in their first scoring system to classify patients: ascites, a neurological illness, serum bilirubin, serum albumin, and clinical nutrition status. Later, Pugh et al. changed the scoring method and replaced clinical nutrition status with prothrombin time. They also added changeable points for each criterion, with points rising in severity. [29]

Ethical approval:

The Declaration of Helsinki's ethical principles were adhered to during the conduct of the study, and on March 17, 2022, The Faculty of Medicine, Ethical Committee of Alexandria University gave its approval with serial number 0107109. All conscious patients gave consent after being informed. First-degree relatives of patients with altered consciousness gave their permission after receiving full details.

Results

1. **Sociodemographic information**

• **Gender**: In the current study, group 1 (n = 40) included: Men made up 42.5% (n = 17), while women made up 57.5% (n = 23). while group 2 (n = 40) had 60.0% (n = 24) men and 40% (n = 16) women. There was no statistically significant gender difference across the two groups (p =0.117).

• **Age**: the patient average age (n=40) was 74.93± 6.88, whereas the controls mean age (n=40) was 72.75± 6.14. There was not a noticeable distinction in age among the two groups (p = 0.190).

• **Occupation:** In group 1, there were 25 without employment (62.5%), 2 employed (5.0%), and 13 retired (32.5%). In group 2, there were 13 (32.5%) retired, 1 (2.5%), and 26 (65.0%) unemployed people. Between the two groups, there was no observable remarkable difference in occupation (p=1.000).

- **Marital status:** Group 1 consisted of 14 (35%) widows, 1 (2.5%) divorcee, 24 (60.0%) married people, and 1 (2.5%) single person. Group 2 contained 11

(27.5%) widows, 1 (2.5%) divorcee, 27 (67.5%) married, and 1 (2.5%) single individual. The two groups' marital status pattern did not significantly differ from one another (p=0.903).

• **Cigarette smoking:** 32 (80.0%) nonsmokers made up Group 1, while 8 (20.0%) were smokers. Group 2 contained 12 smokers (30.0%) and 28 non-smokers (70.0%). The two groups' smoking patterns did not significantly differ from one another (p=0.302)

Table [1] displays the Sociodemographic information of the study.

	Group 1 (n = 40)		Group 2 (n = 40)		Test of Sig.	p
	No.	%	No.	%		
Sex						
Male	17	42.5	24	60.0	χ^2= 2.452	0.117
Female	23	57.5	16	40.0		
Age (/years)						
Min. – Max.	66.0 – 85.0		65.0 – 91.0		U= 664.0	0.190
Mean ± SD.	74.93 ± 6.88		72.75 ± 6.14			
Median (IQR)	74.0 (68.0 – 81.0)		71.0 (68.0 – 75.50)			
Occupation						
Unemployed	25	62.5	26	65.0	χ^2= 0.453	^{MC}p= 1.000
Employed	2	5.0	1	2.5		
Retired	13	32.5	13	32.5		
Marital status						
Single	1	2.5	1	2.5	χ^2= 1.027	^{MC}p= 0.903
Married	24	60.0	27	67.5		
Divorced	1	2.5	1	2.5		
Widow	14	35.0	11	27.5		
Smoking						
Non-smoker	32	80.0	28	70.0	χ^2= 1.067	0.302
Smoker	8	20.0	12	30.0		

IQR: **Inter quartile range** SD: **Standard deviation** **U: Mann Whitney test.**
χ^2: **Chi-square test** MC: **Monte Carlo**
p: p-value for comparing the two studied groups.
Group 1: Cirrhotic patients due to HCV including HE
Group 2: Cirrhotic patients due to HCV but no HE is included.

2. Comorbidity

Group 1 included 12 (30%) cardiac patients, 40 (100%) hepatic patients, 21 (52.5%) diabetic patients, and 21 (52.5%) hypertensive patients. In group 2, there were 40 (100%) hepatic, zero renal, 6 (15%) cardiac, 10 (25%) hypertensive, and 11 (27.5%) diabetic individuals. Significant differences were among the two groups for diabetes and hypertension (p=0.022 and p=0.012, respectively). Group 1, the score was noticeably higher.

Table [2] Co-morbidity comparison between the two groups under the study.

	Group 1 (n = 40)		Group 2 (n = 40)		χ^2	p
	No.	%	No.	%		
Diabetes	21	52.5	11	27.5	5.208*	0.022*
Hypertension	21	52.5	10	25.0	6.373*	0.012*
Hepatic	40	100.0	40	100.0	–	–
Renal	0	0.0	0	0.0	–	–
Cardiac	12	30.0	6	15.0	2.581	0.108

3. Clinical presentation

Table [3] Comparing the clinical presentations between the two research groups.

	Group 1 (n = 40)		Group 2 (n = 40)		χ^2	p
	No.	%	No.	%		
Hematemesis & melena						
No	13	32.5	16	40.0	0.487	0.485
Yes	27	67.5	24	60.0		
UGIE & EBL						
No	21	52.5	23	57.5	0.202	0.653
Yes	19	47.5	17	42.5		
Jaundice						
No	25	62.5	32	80.0	2.990	0.084
Yes	15	37.5	8	20.0		
Ascites						
No	11	27.5	22	55.0	7.309	$^{MC}p=0.048$
Mild	1	2.5	2	5.0		
Moderate	20	50.0	11	27.5		
Tense	8	20.0	5	12.5		
Paracentesis						
No	31	77.5	35	87.5	1.385	0.239
Yes	9	22.5	5	12.5		

UGIE & EBL: Upper Gastro-intestinal endoscopy &Esophageal band ligation

Table [4] Compared Complete blood count in the research groups.

	Group 1 (n = 40)	Group 2 (n = 40)	Test of Sig.	p
HB(g/dl)				
Min. – Max.	4.40 – 12.90	5.10 – 13.60		
Mean ± SD.	8.15 ± 2.28	9.08 ± 2.22	t= 1.851	0.068
Median (IQR)	7.45 (6.45 – 10.35)	8.65 (7.40 – 10.95)		
Platelets (×10^3/ UL)				
Min. – Max.	13.0 – 444.0	42.0 – 493.0		
Mean ± SD.	132.3 ± 89.07	155.7 ± 109.8	U= 722.50	0.456
Median (IQR)	109.5 (66.0 – 170.0)	116.0 (74.0 – 211.0)		
WBCs (×10^3/ UL)				
Min. – Max.	1.95 – 24.60	3.17 – 15.0		
Mean ± SD.	9.70 ± 4.88	6.55 ± 3.09	U= 445.0*	0.001*
Median (IQR)	9.18 (6.25 – 11.63)	5.15 (4.47 – 7.91)		

WBCs: White Blood Cells, HB: Hemoglobin

Table [5] The liver function tests are used to compare the research groups.

	Group 1 (n = 40)	Group 2 (n = 40)	Test of Sig.	p
Serum albumin(gm/dl)				
Min. – Max.	2.0 – 4.0	2.0 – 4.30		
Mean ± SD.	2.71 ± 0.45	3.11 ± 0.56	t= 3.511*	0.001*
Median (IQR)	2.70 (2.35 – 2.95)	3.10 (2.80 – 3.44)		
T.S.B (mg/dl)				
Min. – Max.	0.10 – 3.30	0.30 – 3.0		
Mean ± SD.	1.79 ± 0.90	1.24 ± 0.78	U= 513.0*	0.006*
Median (IQR)	1.75 (1.20 – 2.55)	1.10 (0.60 – 1.60)		
ALT (U/L)				
Min. – Max.	9.0 – 456.0	8.0 – 173.0		
Mean ± SD.	47.13 ± 72.77	39.82 ± 40.26	U= 765.0	0.736
Median (IQR)	31.0 (15.0 – 48.0)	24.50 (16.50 – 40.0)		
AST (U/L)				
Min. – Max.	11.0 – 509.0	16.0 – 406.0		
Mean ± SD.	75.65 ± 89.06	69.33 ± 81.16	U= 731.0	0.507
Median (IQR)	46.0 (31.0–82.50)	37.0 (24.0–79.50)		

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, T.S.B: Total serum bilirubin,

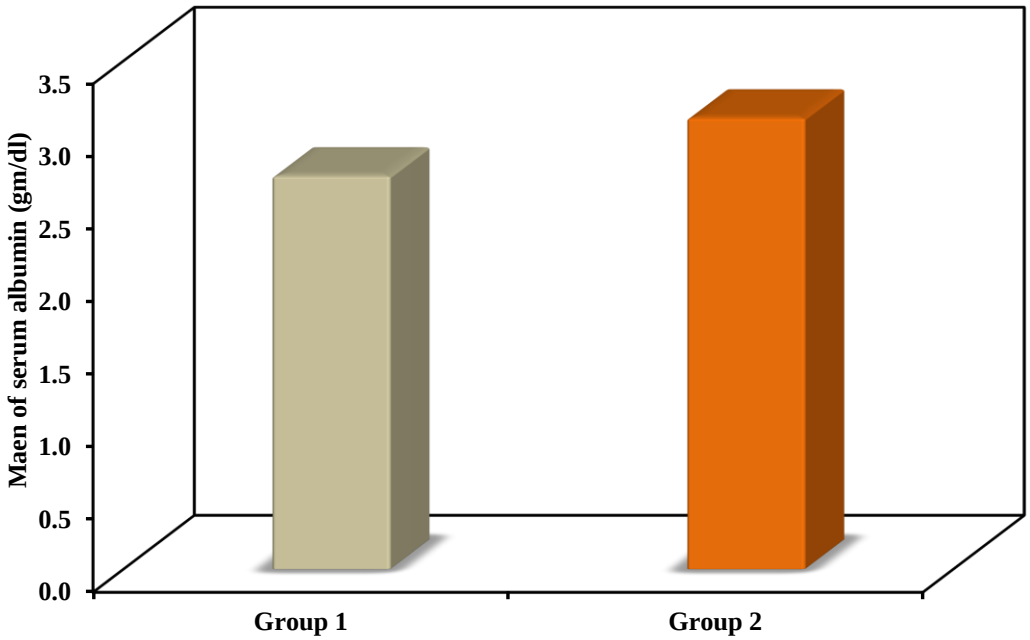

Figure [1] Serum albumin to compare the two groups in the research.

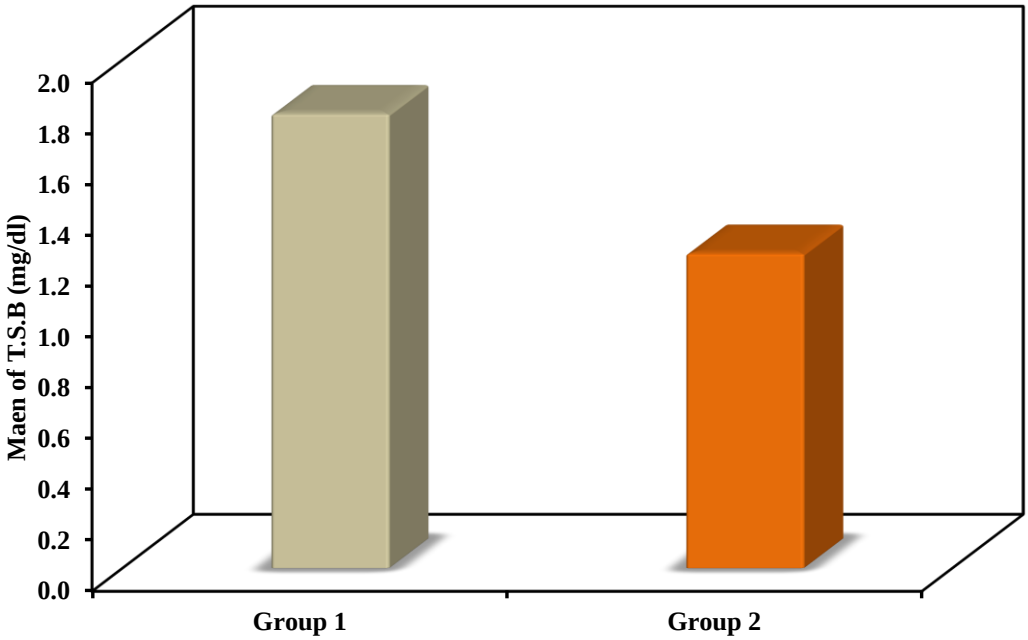

Figure [2] T.S.B. compared the two research groups.

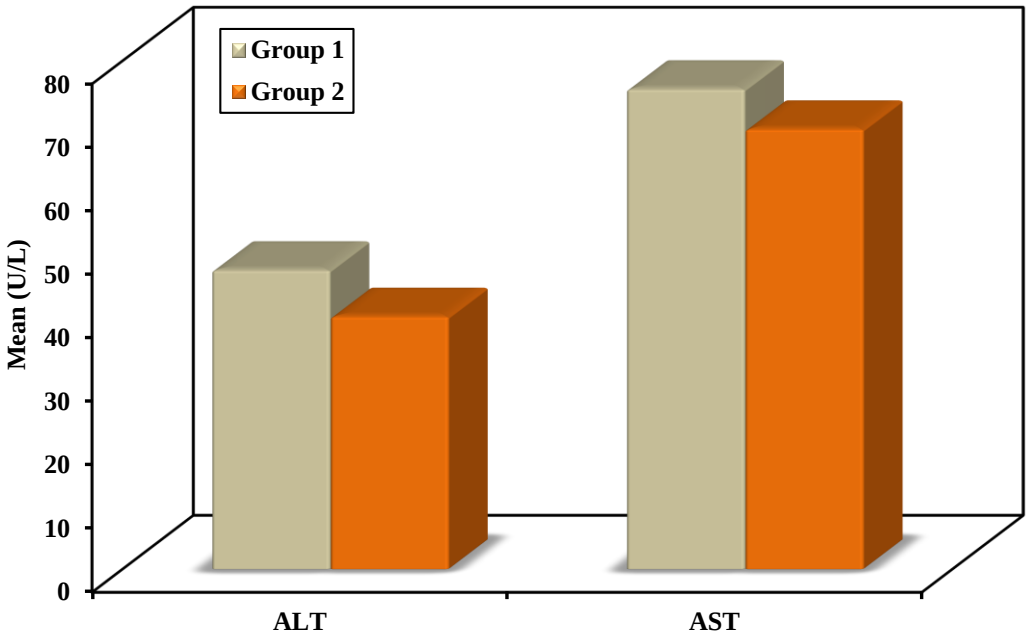

Figure [3] Comparison of the two groups under investigation using ALT and AST

6. Renal function tests

Blood urea in group 1, blood urea levels varied from 11.0 to 49.0, with S.D of 32.65 ± 9.08. The range of blood urea in group 2 was 19.0–45.0, with S.D of 32.71± 6.93. No obvious distinction could be made across the research groups (p = 0.972).

- **Creatinine in serum**

The range of serum creatinine in group 1 was 0.50 to 1.30, with an average value (S.D.) of 0.89± 0.26. The range of serum creatinine in group 2 was 0.33 to 1.20, with an average value (S.D.) of 0.83± 0.25. The two groups under study did not differ significantly from one another. (p = 0.324).

- **Uric acid**

In group 1, the uric acid range was 3.0–9.0, with S.D of 4.88±1.58.

In group 2, the uric acid range was 2.60–8.0, with S.D of 4.39± 1.38. No obvious distinction could be made between the two research groups (p = 0.151).

- **Creatinine clearance (CrCl)**

In group 1, CrCl values varied from 62.66 to 99.17, with a mean value (S.D.) of 76.43 ± 11.17. In group 2, CrCl values varied from 65.0 to 127.50, with a mean value (S.D.) of 85.86 ± 19.49. No obvious distinction could be made across the two research groups (p = 0.060).

Table [6] The two studies are compared using renal function testing.

	Group 1 (n = 40)	Group 2 (n = 40)	Test of Sig.	p
Urea (mg/dl)				
Min. – Max.	11.0 – 49.0	19.0 – 45.0		
Mean ± SD.	32.65 ± 9.08	32.71 ± 6.93	t= 0.035	0.972
Median (IQR)	32.50 (27.0 – 40.0)	31.0 (27.0 – 39.50)		
Creatinine (mg/dl)				
Min. – Max.	0.50–1.30	0.33–1.20		
Mean ± SD.	0.89± 0.26	0.83± 0.25	t= 0.994	0.324
Median (IQR)	0.90 (0.69 – 1.10)	0.90 (0.60 – 1.0)		
Uric acid				
Min. – Max.	3.0 – 9.0	2.60– 8.0		
Mean ± SD.	4.88 ± 1.58	4.39 ± 1.38	U= 652.50	0.151
Median (IQR)	4.85 (3.80–5.35)	4.0 (3.0–5.10)		
CRCL				
Min. – Max.	62.66–99.17	65.0 – 127.5		
Mean ± SD.	76.43 ± 11.17	85.86 ± 19.49	U= 605.0	0.060
Median (IQR)	71.42 (68.06–86.18)	83.36 (69.44 – 101.5)		

CrCl: Creatinine clearance.

7. Electrolytes

• Sodium (Na)

The range of Na in group 1 was between 114.0 and 147.0, with S.D of 135.1± 6.12. The range of Na in group 2 was between 124.0 and 145.0, with S.D of 136.4±5.05. There were no remarkable differences among the two research groups (p = 0.322).

- **Potassium (K)**

The mean value (S.D.) for potassium (K) in group 1 was 4.10±0.87, with a range of 2.50 - 6.20. K in group 2 had a range of 2.90 to 5.20 and a mean value (S.D.) of 4.15±0.51 in this group. The two studied groups did not change remarkably from one another (p = 0.790).

Table [7] Electrolytes to compare the two research groups.

Electrolytes	Group 1 (n = 40)	Group 2 (n = 40)	t	p
Na (mmol/L)				
Min. – Max.	114.0 – 147.0	124.0 – 145.0		
Mean ± SD.	135.1±6.12	136.4 ±5.05	0.997	0.322
Median (IQR)	135.5 (131.5 – 139.0)	137.0 (133.5 – 139.5)		
K (mmol/L)				
Min. – Max.	2.50 – 6.20	2.90 – 5.20		
Mean ± SD.	4.10 ± 0.87	4.15 ± 0.51	0.267	0.790
Median (IQR)	3.85 (3.50 – 4.60)	4.10 (3.85 – 4.50)		

Na: Sodium, k: Potassium

8. coagulation profile

- **PT**

  The mean (S.D.) for group 1: PT was 18.56±4.74, with a range of 12.40 to 34.60. The PT ranged from 11.0 to 23.10 in group 2, with a mean value (S.D.) of 15.52±3.09. The two study groups differed markedly from one another (p = 0.001). In group 1, PT was substantially higher.

- **PTT**

  PTT for group 1 had a mean value (S.D.) of 45.01±14.54 with a range of 29.10 to 89.60. PTT for group 2 had a range of 24.10–77.0 and a mean

value (S.D.) of 40.45±11.54. No noticeable variations existed between the two research groups (p = 0.167).

- **INR**

In group 1, the INR range from 1.09 to 3.35, with S.D of 1.67± 0.49.

Group 2, INR had a range of 0.96 to 2.06 with S.D of 1.36± 0.27. Among the two research groups, there was a noteworthy distinction (p 0.001). INR in group 1 was substantially higher.

Table [8] Comparison of the coagulation profiles of the study.

	Group 1 (n = 40)	**Group 2 (n = 40)**	**U**	**p**
PT (sec.)				
Min. – Max.	12.40 – 34.60	11.0 – 23.10		
Mean ± SD.	18.56 ± 4.74	15.52 ± 3.09	449.50*	0.001*
Median (IQR)	17.95 (15.0 – 21.0)	14.50 (13.20 – 17.35)		
PTT (sec.)				
Min. – Max.	29.10 – 89.60	24.10 – 77.0		
Mean ± SD.	45.01 ± 14.54	40.45 ± 11.54	656.50	0.167
Median (IQR)	40.05 (34.45 – 51.85)	37.90 (32.15 – 46.65)		
INR				
Min. – Max.	1.09 – 3.35	0.96 – 2.06		
Mean ± SD.	1.67 ± 0.49	1.36 ± 0.27	425.0*	<0.001*
Median (IQR)	1.57 (1.32 – 1.82)	1.27 (1.16 – 1.51)		

PTT: Partial thromboplastin time, PT: Prothrombin time, and INR: International normalized ratio

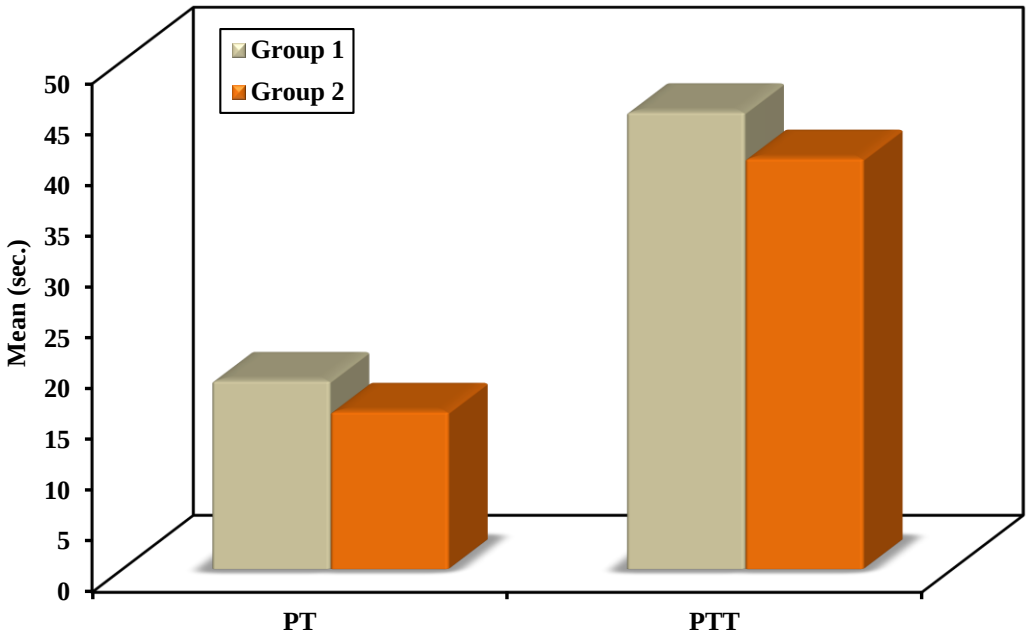

Figure [4] Utilizing PT and PTT to compare the results of the two research groups.

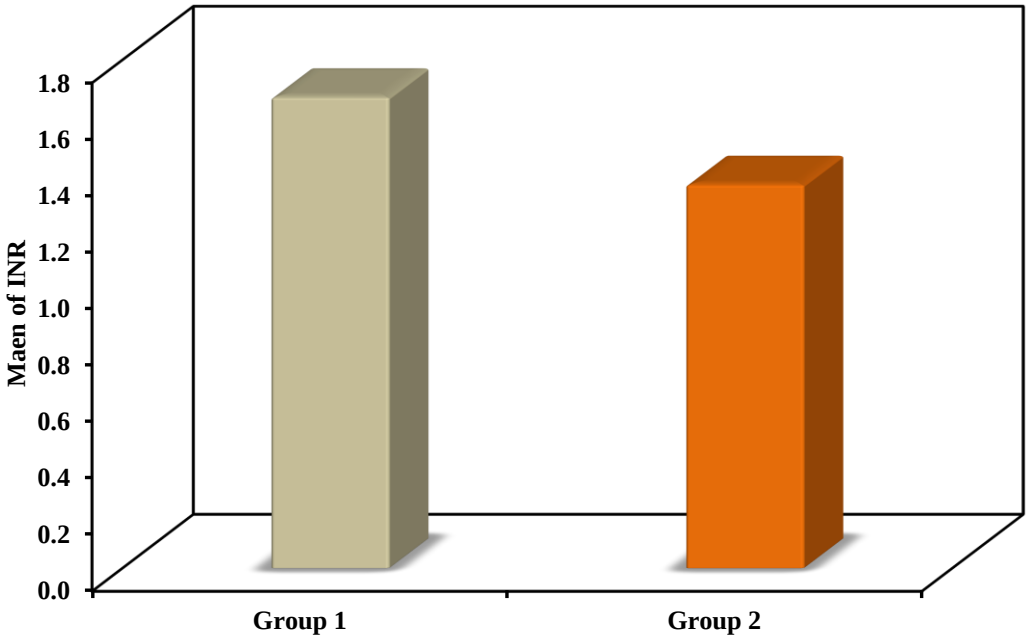

Figure [5] Based on INR, comparing the two research groups.

9. Vitamin D 25-OH levels in the blood

In group 1, vitamin D concentrations range from 3.0 to 42.0, with S.D of 10.68±7.43. The range of vitamin D in group 2 was 3.0 to 75.0, with S.D

of 13.03±10.85. Despite their being a S.D. difference, the data indicated a lack of statistical significance among the two research groups (p = 0.085).

Table [9] Comparing the two research groups depending on serum 25-OH vitamin-D concentration.

	Group 1 (n = 40)	Group 2 (n = 40)	U	p
Serum level of 25-OH vitamin-D (ng/ml)				
Min. – Max.	3.0 – 42.0	3.0 – 75.0		
Mean ± SD.	10.68 ± 7.43	13.03 ± 10.85	621.50	0.085
Median (IQR)	8.50 (6.0–14.50)	11.0 (8.50 – 15.0)		

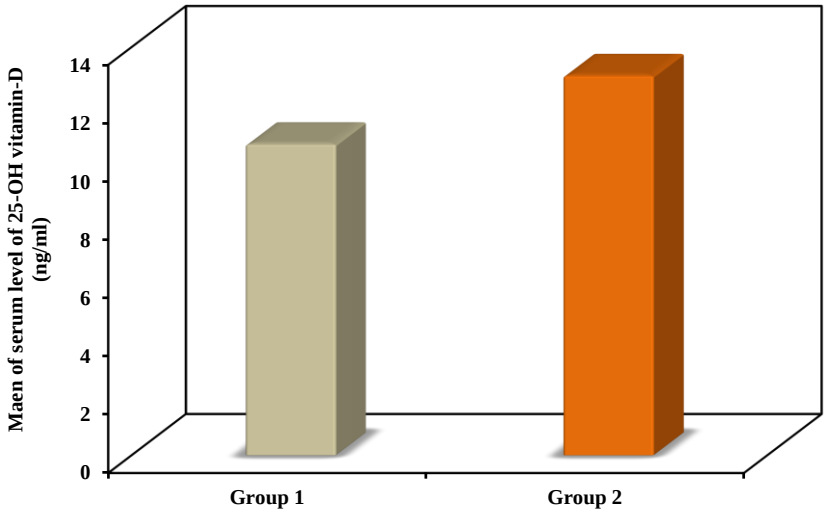

Figure [6] Comparing the research groups based on serum levels of 25-OH vitamin-D.

Table [10] Distribution of the cases under study in group 1 (HCV-related cirrhotic patients with HE)(n = 40) according to the West Haven criteria

	No.	%
West Haven criterion		
Grade I	13	32.5
Grade II	9	22.5
Grade III	8	20.0
Grade IV	10	25.0

10. Child Turcotte Pugh score (CTP score)

The CTP score for group 1 was 7.0 to 13.0, with S.D of 9.70±1.60.

The CTP score for group 2 was 5.0–10.0, with S.D of 6.93±1.40. Among the two research groups, there was a noteworthy distinction (P = 0.001). Group 1 had a much higher CTP score.

Table [11]Comparison of the CTP scores in the study.

	Group 1 (n = 40)	Group 2 (n = 40)	U	p
CTP score				
Min. – Max.	7.0 – 13.0	5.0 – 10.0		
Mean ± SD.	9.70 ± 1.60	6.93 ± 1.40	162.0*	<0.001*
Median (IQR)	10.0 (9.0 – 10.50)	7.0 (6.0 – 8.0)		

CTP : Child Turcotte Pugh

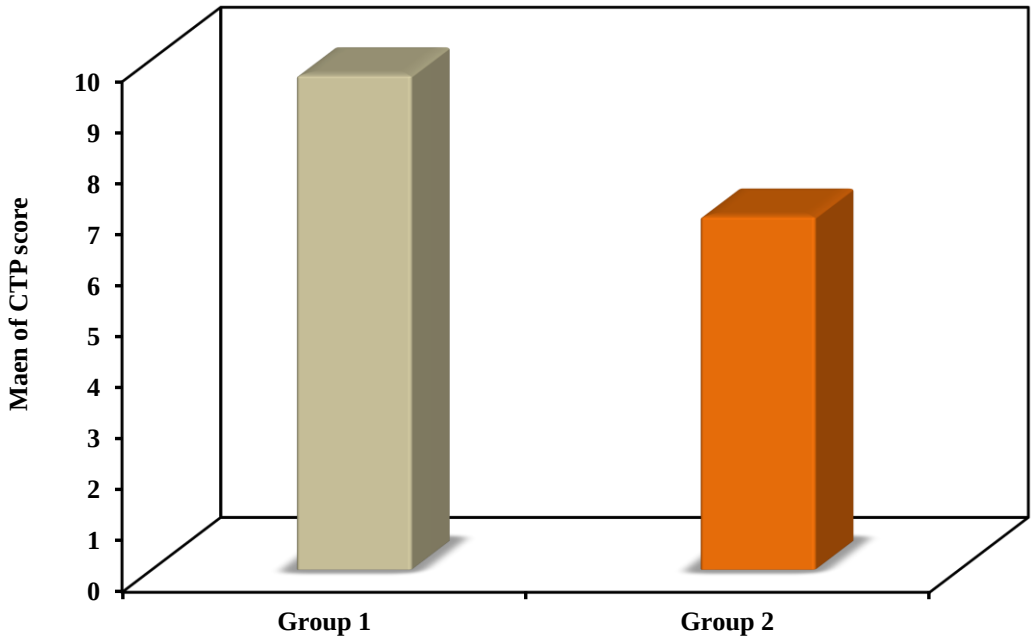

Figure [7] Comparison of the CTP scores in the study

11. Model for End-stage liver disease (MELD) score and Model for End-Stage Liver Disease – Sodium (MELD-Na) score

- **Regarding MELD score:**

MELD score for group 1 was 7.0 to 24.0, with S.D of 14.40±3.95. Group 2, MELD score varied from 6.0 to 18.0 with S.D of 11.05±3.23. There was a noteworthy discrepancy across the two research groups (p 0.001). Group 1 showed a significantly greater MELD score.

Regarding the MELD-Na score:

The MELD-Na score for group 1, varied from 7.0 to 27.0, with S.D of 17.58±5.15. Group 2, MELD-Na score was from 8.0 to 25.0, with S.D of 14.10±4.51. A considerable difference existed between the two research groups (p 0.002). Group 1 showed a significantly greater MELD-Na score.

Table [12] Comparing the MELD score and MELD-Na for the study.

	Group 1 (n = 40)	Group 2 (n = 40)	t	p
MELD score				
Min. – Max.	7.0 – 24.0	6.0 – 18.0		
Mean ± SD.	14.40±3.95	11.05±3.23	4.148*	<0.001*
Median (IQR)	14.0 (12.0 – 16.50)	11.0 (8.0 – 13.0)		
MELD-Na				
Min. – Max.	7.0 – 27.0	8.0 – 25.0		
Mean ± SD.	17.58±5.15	14.10±4.51	3.211*	0.002*
Median (IQR)	17.0 (14.0 – 21.50)	14.0 (10.50 – 17.50)		

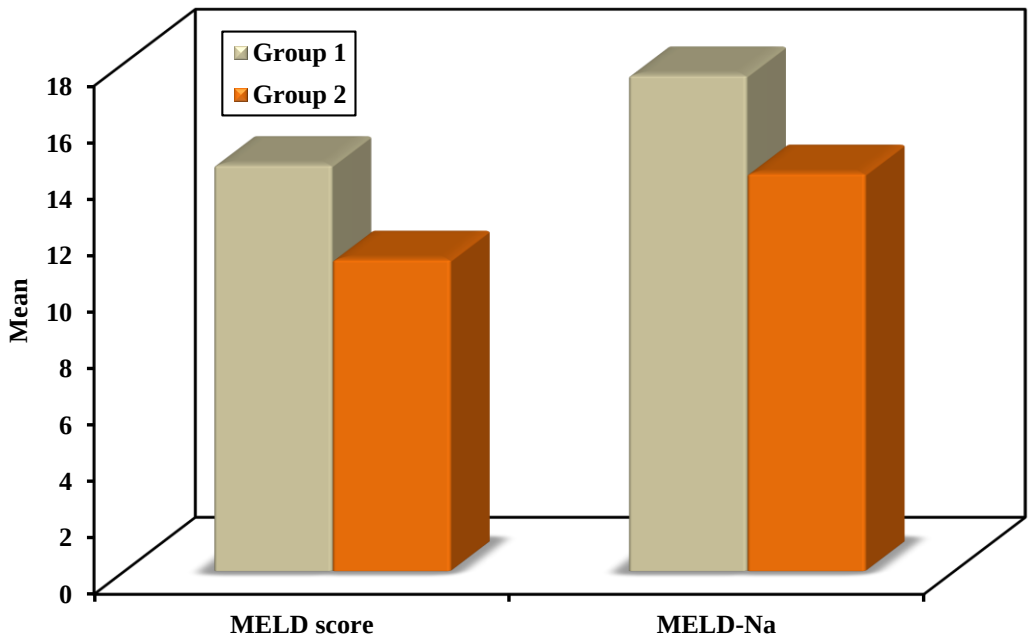

Figure [8] Comparing the MELD score and MELD-Na in the study.

12. 25-OH vitamin-D levels in serum, biochemical variables, CTP, and MELD scores

In group 1 (HCV-related cirrhotic patients with HE), table (13) demonstrates the interactions between blood levels of 25-OH vitamin-D and biochemical variables, CTP scores, and MELD scores.

- Vitamin D and T.S.B demonstrated a statistically noteworthy negative correlation (r = -0.495, p = 0.001).
- Vitamin D and Na were shown to be positively correlated (r = 0.501, P = 0.001) statistically.
- Additionally, vitamin D and PT had a statistically remarkable negative connection. (r = -0.397, p = 0.011), INR (r = -0.405, P = 0.009), CTP score (r = -0.374, p = 0.017), MELD score (r = -0.455, P = 0.003), and MELD-Na score (r = -0.539, p 0.001).
- Other research variables in table [13], however, did not exhibit a statistically significant link with vitamin D.

Table [13] Correlation between biochemical variables, CTP scores, and MELD scores and serum levels of 25-OH vitamin-D in group 1 (cirrhotic patients due to HCV including HE) (n = 40)

Serum level of 25-OH vitamin-D (ng/ml) vs.	r_s	p
HB (g/dl)	0.149	0.360
Platelets ($\times 10^3$/ UL)	0.000	0.998
WBCs ($\times 10^3$/ UL)	-0.107	0.510
Serum albumin (gm/dl)	0.118	0.470
T.S.B (mg/dl)	-0.495	0.001*
ALT (U/L)	0.184	0.256
AST (U/L)	0.144	0.375
Urea (mg/dl)	-0.026	0.876
Creatinine (mg/dl)	0.122	0.455
Na (mmol/L)	0.501	0.001*
K (mmol/L)	-0.090	0.581
PT (sec.)	-0.397	0.011*
PTT (sec.)	0.080	0.625
INR	-0.405	0.009*
CTP score	-0.374	0.017*
MELD score	-0.455	0.003*
MELD-Na	-0.539	<0.001*

rs: Spearman coefficient

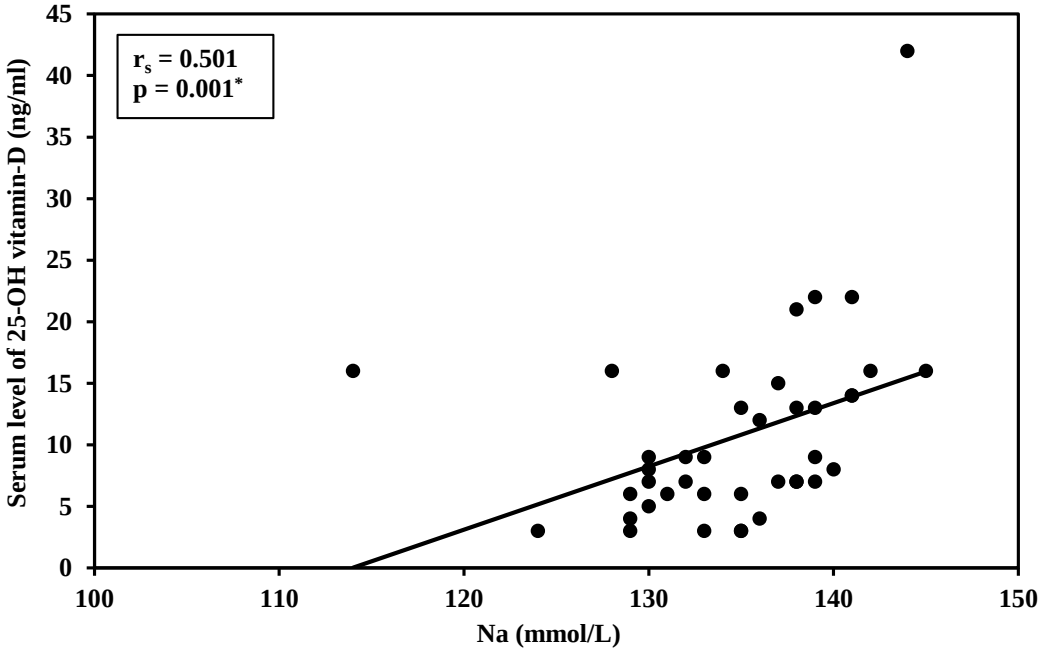

Figure [9] Correlation between group 1's (Cirrhotic patients due to HCV including HE) serum level of 25-OH vitamin-D and Na (mmol/L) (n = 40)

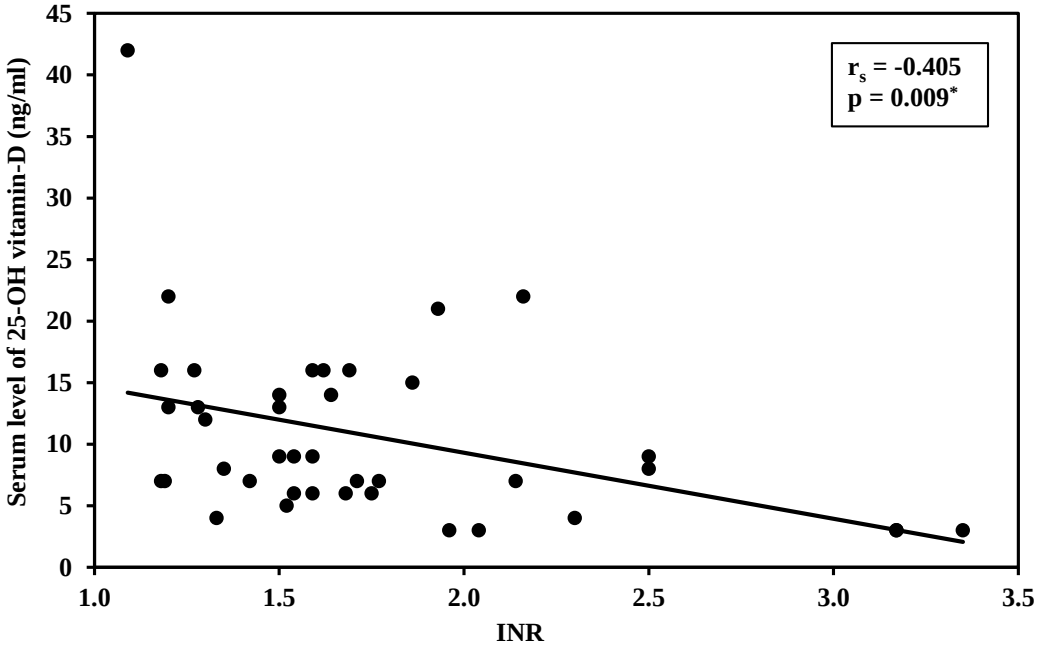

Figure [10] Correlation between group 1 (cirrhotic patients due to HCV including HE) INR and blood levels of 25-OH vitamin-D (n = 40)

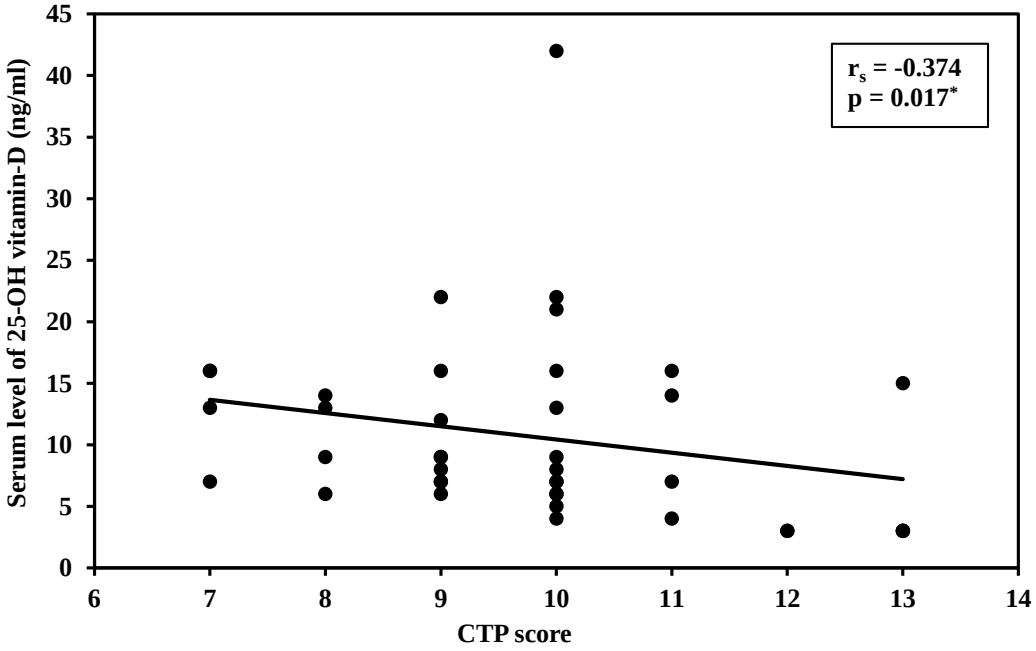

Figure [11] Correlation between group 1(cirrhotic patients due to HCV including HE) CTP score and blood level of 25-OH vitamin-D (n = 40)

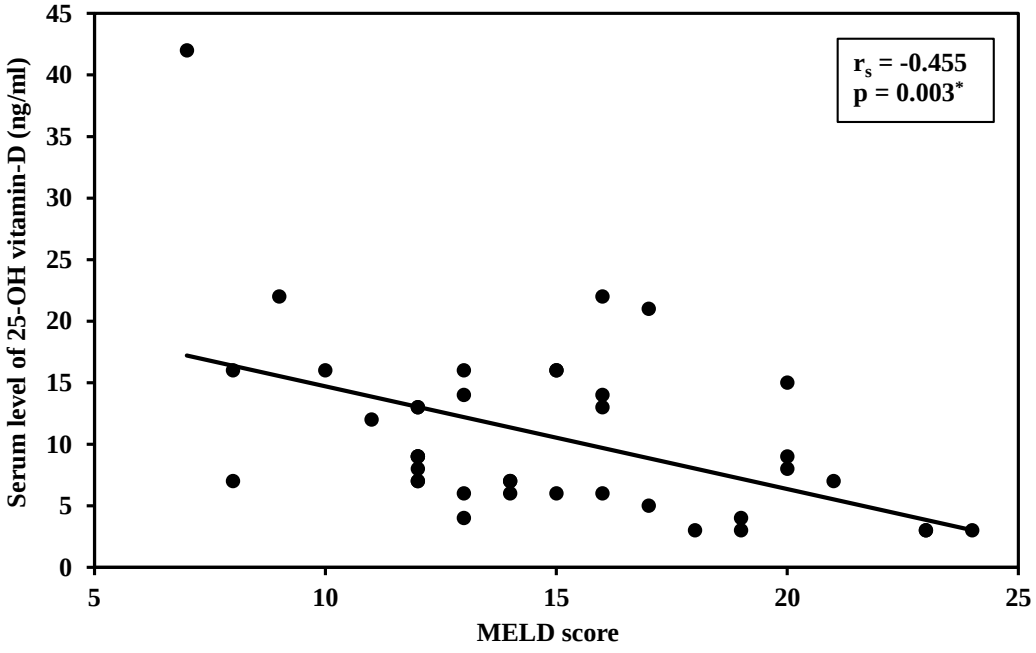

Figure [12] Correlation between group 1 (cirrhotic patients due to HCV including HE) MELD score and blood level of 25-OH vitamin-D (n = 40)

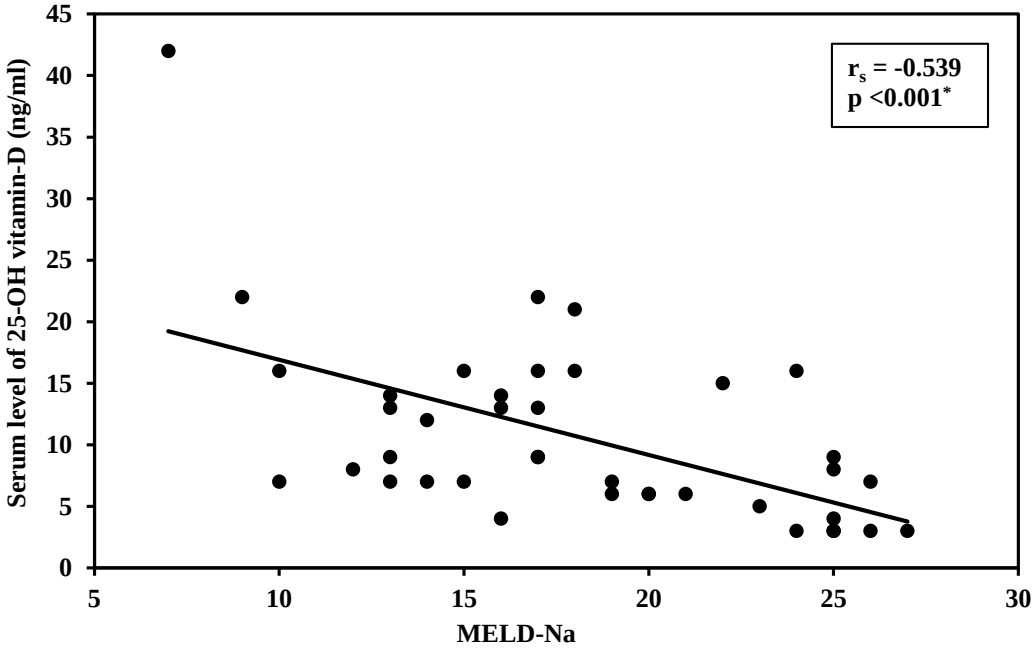

Figure (13): Correlation between group 1's (cirrhotic patients due to HCV including HE) MELD-Na and blood levels of 25-OH vitamin-D (n = 40)

Blood levels of 25-OH vitamin D and the West Haven criteria

In group 1 (cirrhotic patients due to HCV including HE), table (14) demonstrates the relation between blood 25-OH vitamin-D levels and the West Haven criteria. Grade I had a greater amount of vitamin D than grade II, which had a higher level than grades III and IV. With a P value of 0.032, A correlation with statistical significance between vitamin D and the West Haven criterion was discovered.

Table [14] Relationship between group 1 (cirrhotic patients due to HCV including HE) blood levels of 25-OH vitamin-D and the West Haven criteria (n = 40)

	No.	blood level of 25-OH vitamin-D (ng/ml)		H	p
		Mean ± SD.	Median (Min. – Max.)		
West Haven criteria					
Grade I	**13**	15.15 ± 9.95	13.0 (6.0 – 42.0)	8.773*	0.032*
Grade II	**9**	10.33 ± 4.82	8.0 (4.0 – 16.0)		
Grade III	**8**	8.63 ± 4.75	7.0 (3.0 – 16.0)		
Grade IV	**10**	6.80 ± 4.44	6.0 (3.0 – 16.0)		

H: H for **Kruskal Wallis test**

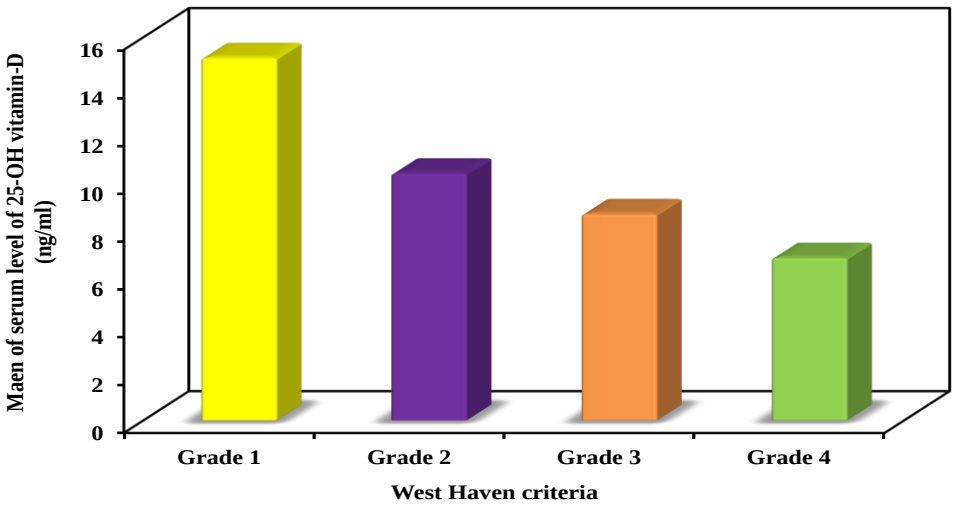

Figure [14] Correlation between group 1 (cirrhotic patients due to HCV including HE) blood 25-OH vitamin-D levels and the West Haven criteria (n = 40)

Discussion

Older people are more vulnerable to the life-threatening cirrhosis complication known as encephalopathy, which may be caused by a dysfunctional brain-gut axis. [30] Lack of 25-hydroxyvitamin D is one of the factors that have recently been found to be connected to hepatic encephalopathy. [26] A few recent investigations have also shown an association between the progression of the disease and the

25-OHD deficiency's worsening. It has been discovered that hepatic encephalopathy patients had reduced amounts of vitamin D than patients not suffering from the condition. [31]

The mean age was 74.93±6.88 for group 1 (cases), and 72.75±6.14 for group 2 (control). Age differences across the two groups were insignificant. (p = 0.190). In the current study, males made up 42.5% of group 1 (cases), females made up 57.5%, and in group 2 (control), males made up 60.0% and females made up 40%. Gender did not differ across the two groups in a statistically meaningful way (p =0.117).

In our research, almost all the patients had a vitamin D deficit status. Blood 25-OH vitamin-D in group 1 was on average 10.68 7.43, whereas levels in group 2 were on average 13.03 10.85. Even though there was a mean difference between the two groups, no observable statistical variation existed in the two groups under investigation (p = 0.085). Due to reduced sun exposure, which in turn results in reduced skin vitamin D production, inadequate nutrition, and problems absorbing vitamin D and/or vitamin D's hepatic 25-hydroxylation, cirrhotic individuals may be more susceptible to reduced 25(OH)D levels. [32]

Many in-depth investigations and trials, in contrast to our work, have shown that individuals with cirrhotic liver were suffering from significant vitamin D deficiency. Zhao *et al* [33], in research of 345 people with cirrhotic liver, discovered that the vitamin D in these patients were remarkably low. In another study carried out in Spain, Fernandez *et al* [34] found that 87 percent of the cirrhotic cases had a vitamin D deficiency. 80 percent of the 160 people with cirrhosis in a different group studied by Kumar *et al* [35] had inadequate amounts of vitamin D.

A statistically remarkable link between vitamin D and the West Haven criterion was discovered in the current investigation (r = -0.374, p = 0.017).

Child A and B had greater levels of 25-OHD than did Child C, indicating a negative relationship between these two parameters., according to Afifi and his colleagues. The study by Fisher *et al*. discovered similar outcomes, with more patients lacking in vitamin D seen in Child C [36,37].

The MELD-Na score and vitamin D also demonstrated a statistically remarkable negative correlation (r = -0.539, p 0.001) in the current study, demonstrating that 25-OHD levels are going to be more inadequate as the disease progresses. When comparing 25-

OH vitamin D to the West Haven criteria in group 1 (cirrhotic patients due to HCV including HE), we discovered that grade I had a greater vitamin D level than grade II, which had a higher level than grades III and IV. With a P value of 0.032, a statistically remarkable association between vitamin D and the West Haven criteria was discovered.

Furthermore, our results concurred with those of other earlier studies indicating a negative correlation between vitamin D and both the CTP and MELD scores [38]. Two studies by Zhao *et al* and Fernandez *et al* revealed that blood levels of vitamin D decrease more rapidly when liver cirrhosis worsens. When compared to people with lower CTP and MELD scores, individuals with greater CTP and MELD scores had considerably lower blood levels of vitamin D.[33,34]

Conclusion

- Most older liver cirrhotic patients have inadequate levels of vitamin D.
- Although a mean difference existed between the two research groups, vitamin D showed no statistically remarkable difference.
- Vitamin D and the MELD-Na score also had a statistically remarkable inverse correlation.
- Vitamin D and the West Haven criterion were found to be statistically significantly correlated.

Recommendations

To confirm our findings and determine if supplementing with vitamin D is useful in preventing and treating liver cirrhosis and hepatic encephalopathy, additional big trials are required.

Finances Sponsorship: None.

No conflicts of interest, according to the authors.

References

[1] UN. Department of Economic and Social Affairs World Population Ageing 2019: Highlights (ST/ESA/SER.A/430) 2019. [(accessed on 16 February2022)].Availableonline:www.un.org/en/development/desa/population/publications/pdf/ageing/WorldPopulationAgeing2019-Highlights.pdf/

[2] United Nations, Department of Economic and Social Affairs, Population Division (2019). World Population Prospects 2019, Online Edition. Rev. 1. Excel files used: Population by broad age groups – male, population by broad age groups – female, percentage by broad age groups – male, percentage by broad age groups – female.https://population.un.org/wpp/Download/Standard/Population/ Accessed 17 May 2023.

[3] In a prospective observational study conducted in the central region of Croatia,

Gunjaa I. and Franceti I. (2010) examined the prevalence and clinical outcome of spontaneous bacterial peritonitis in hospitalized patients with liver cirrhosis. 49(1):11–8, Acta Clin Croat.

[4] A multicenter, retrospective cohort research involving 1124 patients found that patients with chronic hepatitis C who had a prolonged virological response to interferon therapy developed hepatocellular cancer. 186–91 in Liver Int., 27(2).

[5] Th abut, D., Le Calvez, S., Thibault, V., Massard, J., Munteanu, M., Di Martino, et al. 6,865 people with hepatitis C who are 65 years or older: a severe, untreated disease? 106(6):1260-70 in Am J Gastroenterol

[6] Yoshiji H, Nagoshi S, Akahane T, Asaoka Y, Ueno Y, et al. (2006). Evidence-based clinical practice guidelines for liver cirrhosis. J Gastroenterol, 56: 593-619.

[7] Lee NY and Suk KT.The Gut Microbiome's Function in the Treatment of Liver Cirrhosis (2020). Int. J. Mol. Sci., 22:199.

[8] Yang JD, Kim WR, Coelho R, Mettler TA, Benson JT, Sanderson SO, and other participants. (2011) The majority of people with hepatitis B and hepatocellular cancer have cirrhosis. 9:64–70 Clin Gastroenterol Hepatol

[9] El-Refai S, Funk AL, Fontanet A, Kandeel A, Genedy M, Talaat M.(2017) Implications for future preventive and therapeutic strategy about the frequency of hepatitis C virus infection in Egypt in 2015. Liver Int., 37: 45–53.

[10] The WHO is a global health organization.2016's Special Tropical Diseases Research and Training Program (TDR). Switzerland's Geneva.

[11] Vilstrup H, Amodio P, Bajaj J, et al.(2014) Hepatic encephalopathy in chronic liver disease: Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology, 60:715–35.

[12] Rai R, Saraswat VA, Dhiman RK.(2015) Gut microbiota: its role in hepatic encephalopathy. J ClinExpHepatol.,5:S29-36.

[13] Guevara M, Baccaro ME, Ríos J, Martín-Llahí M, Uriz J, Ruiz del Arbol L, et al.(2010) Risk factors for hepatic encephalopathy in patients with cirrhosis and refractory ascites: relevance of serum sodium concentration. Liver Int., 30:1137-42.

[14] Bémeur C, Butterworth RF.(2014) Nutrition in the management of cirrhosis and its neurological complications. J ClinExpHepatol., 4:141-50.

[15] Teperman LW.(2013) Impact of pretransplant hepatic encephalopathy on liver posttransplantation outcomes. Int J Hepatol., 9:528-28.

[16] Bémeur C, Butterworth RF.(2014) Nutrition in the management of cirrhosis and its neurological complications. J Clin Exp Hepatol., 4:141-50.

[17] Vidot H, Potter A, Cheng R, Allman-Farinelli M, Shackel N.(2017) Serum 25-hydroxyvitamin D deficiency and hepatic encephalopathy in chronic liver disease. World J Hepatol., 9:510-8.

[18] Borella E, Nesher G, Israeli E, Shoenfeld Y.(2014) Vitamin D: A new anti-infective agent? Ann N Y Acad Sci.,1317:76-83.

[19] Buell JS, Dawson-Hughes B.(2008) Vitamin D, and neurocognitive dysfunction: Preventing "D" decline? Mol Aspects Med., 29:415-22.

[20] McCann JC, Ames BN. (2008) Is there convincing biological or behavioral evidence linking vitamin D deficiency to brain dysfunction? FASEB J, 22:982-1001.

[21] Eyles DW, Burne TH, McGrath JJ. (2013) Vitamin D, effects on brain development, adult brain function, and the links between low levels of vitamin D and neuropsychiatric disease. Front Neuroendocrinol., 34:47-64.

[22] Christakos S, Ajibade DV, Dhawan P, Fechner AJ, Mady LJ.(2010) Vitamin D: metabolism. Endocrinol Metab Clin North Am., 39:243-53.

[23] Borella E, Nesher G, Israeli E, Shoenfeld Y.2014) Vitamin D: a new anti-infective agent? Ann N Y Acad Sci., 1317:76-83.

[24] Arteh J, Narra S, Nair S.(2010) Prevalence of vitamin D deficiency in chronic liver disease. Dig Dis Sci., 55:2624-8.

[25] Malham M, Jørgensen SP, Ott P, Agnholt J, Vilstrup H, Borre M, et al.(2011) Vitamin D deficiency in cirrhosis relates to liver dysfunction rather than etiology. World J Gastroenterol., 17:922-5.

[26] Stokes CS, Krawczyk M, Reichel C, Lammert F, Grünhage F.(2014) Vitamin D deficiency is associated with mortality in patients with advanced liver cirrhosis. Eur J Clin Invest., 44:176-83.

[27] Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al.(2014) Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology, 60:715-35.

[28] Kamath PS, Kim WR.(2007) The model for end-stage liver disease (MELD). Hepatology, 45:797-805.

[29] Peng Y, Qi X, Guo X.(2016) Child-Pugh Versus MELD Score for the Assessment of Prognosis in Liver Cirrhosis: A Systematic Review and Meta-Analysis of Observational Studies. Medicine (Baltimore), 95:e2877.

[30] Bajaj JS, Ahluwalia V, Steinberg JL, Hobgood S, Boling PA, Godschalk M, Habib S, White MB, Fagan A, Gavis EA, Ganapathy D, Hylemon PB, Stewart KE, Keradman R, Liu EJ, Wang J, Gillevet PM, Sikaroodi M, Moeller FG, Wade JB.(2016) Elderly patients have an altered gut-brain axis regardless of the presence of cirrhosis. Sci Rep., 6:38481.

[31] Kubesch A, Quenstedt L, Saleh M, Rüschenbaum S, Schwarzkopf K, Martinez Y, et al.(2018) Vitamin D deficiency is associated with hepatic decompensation and inflammation in patients with liver cirrhosis: A prospective cohort study. PLoS One, 13:e0207162.

[32] Zuniga S, Firrincieli D, Housset C, Chignard N.(2011) Vitamin D and the vitamin D receptor in liver pathophysiology. Clin Res Hepatol Gastroenterol., 35: 259–302.

[33] Zhao XY, LiJ, Wang JH, Habib S, Wei W, Sun SJ, et al.(2016) Vitamin D serum levels associated with Child-Pugh score and metabolic enzyme imbalances, but not viral load in chronic hepatitis B patients. Medicine (Baltimore), 95:e3926.

[34] Fernández NF, Torres PL, Matias DJ, Plaza FJ, Goñi JL.(2016) Vitamin D deficiency in chronic liver disease, clinical epidemiological analysis, and report after vitamin D supplementation. Gastroenterología y Hepatología (English Edition), 1;39(5):305-10.

[35] Kumar R, Kumar P, Saxena KN, Mishra M, Mishra VK, Kumari A, et al.(2017) Vitamin D status in patients with cirrhosis of the liver and their relatives' case-control study from North India. Indian J Gastroenterol., 36:50–55.

[36] MAE.Afifi, AM.Hussein, M. Rizk. (2021) Low Serum 25-Hydroxy Vitamin D (25-OHD) and Hepatic Encephalopathy in HCV-Related Liver Cirrhosis. Int J Hepatol. vol.9(2), pp.2-8.

[37] L.Fisher, A.Fisher.(2007) Vitamin D and parathyroid hormone in outpatients with non-cholestatic chronic liver disease. Clin Gastroenterol Hepatol.vol.5(4),pp.513–20.

[38] C.Konstantakis, P.Tselekouni, M.Kalafateli, C.Triantos.(2016) Vitamin D deficiency in patients with liver cirrhosis. Ann Gastroenterol Q Publ Hell Soc Gastroenterol.vol.29(3),pp.297.