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Diagnostic Significance of Serum Serotonin Levels in Prediction of Esophageal and Fundal Varices in Cirrhotic Patients

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Abstract

Background: Serotonin known to be a neurotransmitter can regulate several key aspects of liver biology.

Aims: This study aimed to determine the role of serum serotonin levels (5-HT) as a non-invasive marker in the prediction of esophageal and fundal varices in cirrhotic patients.

Patients and Methods: The study included seventy cirrhotic patients with hepatitis C virus and fifteen apparently healthy subjects as a control group. Patients were further sub-classified according to upper Gastrointestinal Endoscopy into three groups: Group A: Included 30 cirrhotic patients without esophageal varices (OV), Group B: Included 29 cirrhotic patients with OV, Group C: Included 11 cirrhotic patients with OV and fundal varices. All subjects were subjected to full history taking, clinical evaluation, routine laboratory investigations and serum-serotonin by ELISA.

Results: The mean level of serum Serotonin showed a gradual increase in cirrhotic patients with the highest level in oesophageal and fundal varices (94.04±8.51ng/ml), followed by patients with oesophagal varices only (39.2±18.38ng/ml), and both groups were significantly increased than the patient group with no oesophageal varices. There was a positive correlation between serum serotonin level and serum creatinine level, presence and grading of oesophagal varices and the presence of fundal varices. Serum serotonin level at a cutoff value 32.2ng/ml had a sensitivity of 72% and a specificity of 60% in prediction of OV in cirrhotic patients but at cutoff level 28.4ng/ml had low sensitivity (55%) and bad specificity (25%) in discrimination between grads of OV, while serum serotonin level at a cutoff value 79.1ng/ml had a sensitivity of 100% and a specificity of 96.6% to diagnose patients with oesophagal and fundal varices. Applying multivariate analysis, serum serotonin level was an independent predictor for oesophagal varices.

Conclusion: Serum serotonin levels could be used as a serum non-invasive marker for the presence of gastro-oesophageal varices, but it could not discriminate between the grades of oesophageal varices.

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Key Words: *Serotonin – Varices – Cirrhosis.*

Introduction

GASTROINTESTINAL bleeding linked to portal hypertension is a severe complication threatening cirrhotic patients **[1]**. The frequency of varices in patients with cirrhosis around 60-80% and the danger of bleeding is 25-35%. The incidence of oesophagal varices rises by nearly 5% per year, and the rate of progression from small to large varices is approximately 5 to 10% per year **[2]**.

Oesophageal variceal hemorrhage is a serious problem in cirrhotic patients due to its mortality risk. Each episode of bleeding has a 30%-50% mortality risk. Also, after the early episode of bleeding the incidence of re-bleeding up to 70% and frequently happens within 6 weeks of the early haemorrhage **[3]**.

All cirrhotic patients without previous variceal bleeding undergo endoscopic screening to detect OV according to guidelines **[4]**.

After screening endoscopy, patients with large varices must be treated to avoid the bleeding while other patients should undergo episodic surveillance endoscopy **[5]**, while endoscopy is invasive procedure, often can't be done due to high cost, contra indications or painful effect on patients mainly whose haven't had any bleeding previously **[6]**.

So, to reduce the need for unnecessary endoscopies in cirrhotic patients without OV many researchers had studied some possible non invasive markers for detection of esophageal varices **[2]**. The hepatic stellate cell membrane contains several receptors whose expression was augmented with the degree of liver engery; to these receptors

diverse vasoconstrictors are bound; one of them is serotonin [7].

Serotonin or 5-Hydroxytryptamine (5-HT) is known to adjust several important aspects of liver biology and these purposes include hepatic blood flow, innervation and wound healing [8]. Changes in concentrations of serotonin have been associated with several pathologic circumstances including hypertension, primary pulmonary hypertension, liver cirrhosis, and psychiatric disorders [9]. The aim of the current study was to determine the level of serum serotonin in patients with esophageal and gastric varices and to evaluate its role as a non-invasive marker in the predicting gastroesophageal varices and its grading.

Subjects and Methods

Subjects:

This prospective case-controlled study was conducted on 70 HCV cirrhotic patients (diagnosis of cirrhosis based on clinical, laboratory and radiological data) admitted to Hepatology, Gastroenterology and Infectious Diseases Department and Internal Medicine Department, Benha University Hospital, in addition to 15 healthy subjects served asa control group in period from December 2016 to January 2018. Patients with aged less than 18 years old, other causes of liver cirrhosis (HBV, AIH, alcohol, metabolic causes), patients with HCC, portal vein or splenic vein thrombosis, patients with schizophrenia, Huntington's disease, duchenne's muscular dystrophy and carcinoid syndrome were excluded from the study.

All patients gave informed written consents for participation in this study and this study was approved by the Ethical Committee of Benha Faculty of Medicine, Benha University according to the World Medical Association Declaration of Helsinki [10].

Methods:

All participants were subjected to:

1- Full history taking and thorough clinical examination.

2- Laboratory investigations.

Sampling:

Ten millilitres venous blood samples were obtained by peripheral venipuncture under aseptic precautions from all subjects. The blood sample obtained was divided as follow: On emilliliter of blood on di-K-EDTA to perform CBC, two milliliters of blood on sodium citrate to perform prothrombin time, two milliliters of blood to perform LFTs and KFTs, five milliliters of blood were taken in plain tube then put in water path at 37C for 30 minutes then centrifuged for 10 minutes then the resultant serum was divided into aliquots. Stored at –20C for measuring serum serotonin level.

Laboratory investigations including:

- Complete blood picture by Sysmex-XP 300, (Sysmex, USA), liver function tests: AST, ALT, bilirubin (total & direct), albumin and kidney function tests (creatinine and urea) were measured by biosystem A-15 auto analyzer, (Barcelona, Spain), Prothrombin Time (PT) by coagulometer 2 instrument, (Analyticon Biotechnologies AG, Germany), HBsAg and HCV Abs by 3rd generation enzyme-linked Immunosorbent Assay (ELISA).
- Measurement of serum serotonin level by kits obtained from the sunredbio company, Shanghai, China. (Lot No.=201712), with a lower limit of detection (7.506ng/mL) and an assay range (8-2000ng/mL). The kit practices a double-antibody sandwich Enzyme-Linked Immunosorbent Assay (ELISA).
- Child turcotte-Pugh score was calculated for all patients [11].
- Abdominal US was done for all patients to confirm cirrhosis criteria, presence or absence of ascites, splenic size, splenic vein diameter, collateral and portal hypertension.
- Upper Gastrointestinal Endoscopy by expert endoscopist using (Olympus GIF-Type Q240-Japan) to detect the presence or absence of oesophagal and/or fundal varices. After upper gastrointestinal tract endoscopy, the patients were classified into 3 groups:

Group A: Included 30 cirrhotic patients without OV, Group B: Included 29 cirrhotic patients with OV, were subdivided according to Alempijevic et al., [12] classification into four grades (grade I-IV). Nine patients having grade I-II, nine patients having grade III and eleven patients having grade IV, Group C: Included 11 patients with fundal varices either extension from oesophagalvarices or isolated [13].

Statistical analysis:

Data were analysed using the statistical program for social sciences, SSPS version 18.0 (Chicago, USA). Quantitative data were expressed as mean ± SD and qualitative data were expressed as frequency and percentage. Independent samples *t*-test of significance was used when comparing two means, Receiver Operating Characteristic (ROC)

curve analysis was used to find the overall predictivity of serum serotonin and find the best cutoff value for detection of OV and fundal varices, along with sensitivity and specificity, univariant analysis was performed for each variable followed by multivariant analysis to detect independent predictors for statistically significant variables. The Mann-Whitney U-test used to compare two nonparametric quantitative variables, $p<0.05$ was considered statistically significant **[14]**.

Results

This study included seventy cirrhotic patients as a diseased group with a mean age of (56.26± 13.68) years, they were 45 females and 40 males from rural areas, in addition to 15 healthy subjects of matched age and sex as a control group. Table (1) showed that the lowest level of HB was found in Group C (8.5±2.47mg/dl) with highly statistically significant difference between all studied groups ($p>0.001$). Platelet count was lower in Group B than other groups with highly statistical difference ($p>0.001$) with no significant difference between Group B and C as regard platelet count. There was highly statistically significant difference between studied groups as regard s.creatinine and liver profile tests except s.bilirubin ($p=0.09$).

The mean serum serotonin level showed a gradual increase in cirrhotic patients with the highest level in patients with oesophageal and fundal varices (94.04±8.51ng/ml), followed by patients with OV only (39.2±18.38ng/ml), and both groups were significantly increased than the patient group with no OV Fig. (1).

Table (1): Comparison between the studied groups as regard to laboratory findings.

Variables	Group A (no.=30)	Group B (no.=29)	Group C (no.=11)	Controls (no.=15)	ANOVA Test*	*p*
	Mean ± SD					
HB (gm/dl)	bcd11.51±0.92	acd10.57±1.4	abd8.58±2.47	abc13.17±0.71	26.8	<0.001
Platelet (c/mm^3)	bd118.9±24.6	ad85.51±17.95	d101.6±42.7	abc364.6±37.3	362.9	<0.001
WBCs (X 1000/cmm)	7.66±3.97	5.75±3.21	8.38±7.69	8.35±3.5	1.82	0.1
S.Creatinine (mg/dl)	d1.3±0.7	d1.3±0.6	d1.6±1.1	abc0.9±0.18	2.8	0.04
ALT (IU/dl)	d39.1±8.5	d40.8±11.7	d37.9±8.8	abc25.5±6	9.5	<0.001
AST (IU/dl)	d41.4±12.3	d45.8±16.3	d41.3±15.9	abc26.1±6.8	7.05	<0.001
T.Bilirubin (mg/dl)	d1.8±2	d1.9±1.4	1.2±0.8	ab0.8±0.2	2.2	0.09
S.Albumin (mg/dl)	bd3.01±0.5	acd2.1±0.52	ad3.12±0.49	abc4.2±0.27	66.5	<0.001
INR	1.2±0.34	cd1.3±0.34	b1.12±0.19	b1.02±0.04	4.1	0.001
PT (second)	d15.6±4.5	d17.7±3.8	14.8±2	ab12.7±0.57	5.3	0.001

*: Post hoc test betweenevery two groups was done using LSD test:
A: Means significant with Group A. C: Means significant with Group C.
B: Means significant with Group B. D: Means significant with Group D.

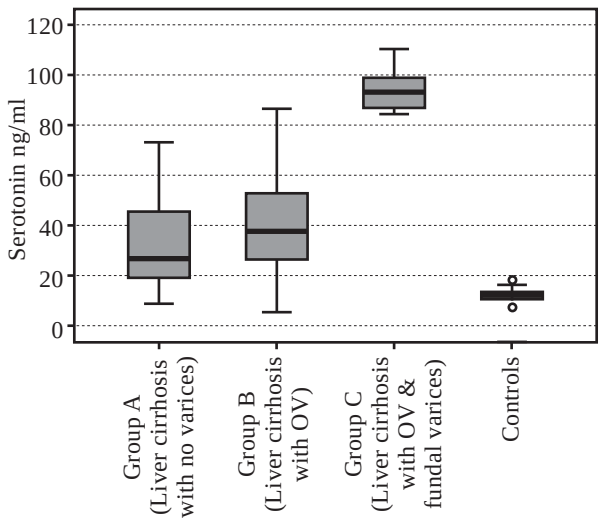


Fig. (1): Box and whisker plot shows a comparison between the studied groups as regard the mean serum serotonin level.

By Child-Pugh classification, 23 patients were Child A, 31 patients were Child B and 16 patients were Child C, therewas no significant difference between Child-Pugh groups regarding serum serotonin level (Table 2). Serum serotonin level was higher in patients with OV (n=29) than patients without OV (n=30), there was a gradual increase in serum serotonin level in accordance with oesophagalvarices grading to reach the highest level in grade IV OV (53.94±9.1ng/ml) and much increased in patients with esophageal and fundal varices (94.04±8.51ng/ml) (Table 3).

There was a highly significant negative correlation between serum serotonin level and both haemoglobin level and platelet count, also a positive correlation between serum serotonin level and serum creatinine level, presence and grading of OV and presence of fundal varices (Table 4).

Serum serotonin level at cutoff value 32.2ng/ml had a sensitivity of 72% and a specificity of 60% and AUC=0.721 to predict OV but its level at cutoff value 79.1ng/ml had high sensitivity reaching 100%

and specificity of 96.6% with AUC=0.99 to differentiate patients with OV and patients had both OV and fundal varices. While serum serotonin level at cutoff value of 28.4ng/ml had low sensitivity (55%) and bad specificity (25%) with AUC=0.27 in the prediction of OV grades (Table 5), Fig. (2A,B,C).

Table (2): Comparison between the Child-Pugh regarding serum serotonin level.

Variable	Serotonin (ng/ml) Mean ± SD	ANOVA Test
Child-Pugh classification:		F=1.32
A (n=23)	49.75±30.77	*p*=0.27 (NS)
B (n=31)	46.62±27.76	
C (n=16)	35.93±17.43	

Table (3): Comparison between the cirrhotic groups graded by upper GIT endoscopy as regard mean level of serum serotonin.

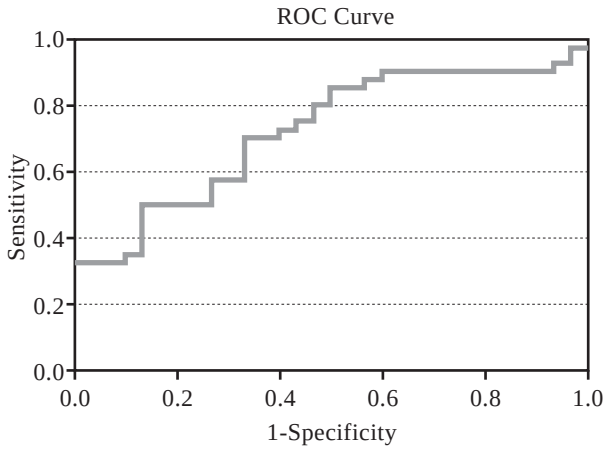
Variable	Serotonin (ng/ml) Mean ± SD	ANOVA Test
Endoscopic findings:		
No OV (n=30)	33.09±17.2 (8.98-73.1)	ANOVA test
OV (n=29)	39.2±18.38 (5.5-86.7)	F=8.99
OV Grade (I-II) (n=9)	29.02±7.05 (15.5-37.8)	*p*=0.001 (HS)
OV Grade (III) (n=9)	31.4±23.3 (5.5-86.7)	F=56.51
OV Grade (IV) (n=11)	53.94±9.1 (42-73.7)	*p*<0.001 (HS)
Fundal varices (n=11)	94.04±8.51 (84.6-110.5)	

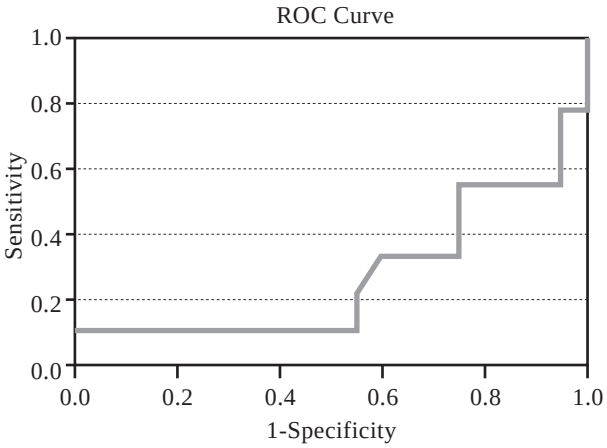
Table (4): Pearson's correlation between serum serotonin level and other parameters among the studied groups.

Serotonin variables	Pearson's correlatio coefficient (*r*)	*p*-value
Age	0.18	0.086
HB (gm/dl)	–0.55	<0.001
Platelet (X 10ml)	–046	<0.001
WBC(X 100/cmm)	0.01	0.86
S. Creatinine (mg/dl)	0.27	0.01
ALT (Iu/dl)	0.14	0.17
AST (Iu/dl)	0.12	0.24
T.bilirubin (mg/dl)	0.01	0.92
S.albumin (g/dl)	–0.15	0.16
INR	0.007	0.94
PT (second)	0.03	0.77
Presence of OV	0.4	0.001
Grading of OV	0.75	<0.001
Presence of fundal varices	0.78	<0.001

Table (5): Diagnostic performance of serum serotonin level to A- Predict Esophageal varices (differentiate between patients with OV and patients without OV), B- Differentiate patients with OV and patients with OV and fundal varices. C- As a marker for prediction of OV grades.

	Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC	*p*-value
A	32.2ng/ml	72%	60%	70.7%	62%	67.1%	0.721	0.002
B	79.1ng/ml	100%	96.6%	91.6%	100%	97.5%	0.99	<0.001
C	28.4ng/ml	55%	25%	25%	55%	35%	0.27	0.06





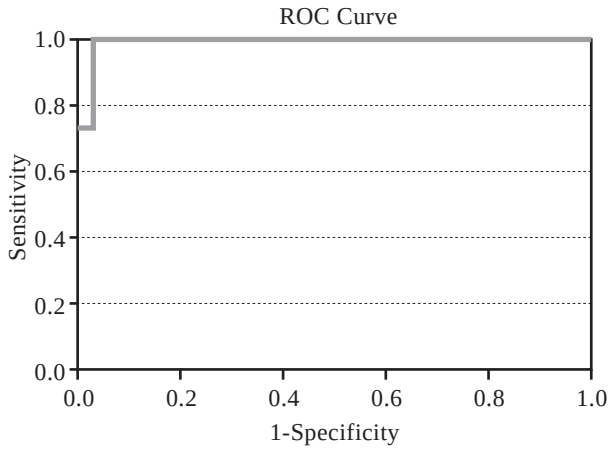


Fig. (1): Box and whisker plot shows a comparison between the studied groups as regard the mean serum serotonin level.

Serum serotonin level, platelet count, HB level and S.creatinine were highly significant predictors of oesophagalvarices in cirrhotic patients by univariate analysis while by multivariate analysis only serum serotonin and HB level were independent predictors for oesophagalvarices (Table 6).

Table (6): Univariate and multivariate analysis for detection of predictors of OV.

Variables	Univariate			Multivariate		
	p	OR	95%CI	*p*	OR	95%CI
Serotonin	<0.001	1.105	1.06-1.14	<0.001	0.55	0.023-0.038
HB gm/dl	<0.001	0.67	0.44-1.01	0.018	–0.17	–0.256- –0.025
Platelet (X 10g/L)	<0.001	1.08	0.91-1.27	0.17	1.083	–0.008-0.003
WBC (X 100/cmm)	0.43	0.97	0.95-0.99			
S.Creatinine (mg/dl)	0.005	0.68	0.21-2.16	0.56	0.68	–1.52-0.77
ALT (Iu/dl)	0.08	0.98	0.91-1.07			
AST (Iu/dl)	0.12	1.04	0.98-1.10			
T.bilirubin (mg/dl)	0.46	0.83	0.5-1.38			
S.albumin (g/dl)	0.08	18.01	5.06-64			
INR	0.47	0.004	0.00-0.68			
PT (second)	0.38	1.74	1.12-2.70			

Discussion

Several studies had evaluated possible non-invasive markers for predicting either the presence of varices or large varices in patients with cirrhosis. The conclusion of most of these studies is that by selecting patients for endoscopic screening based on a few clinical, laboratory and/or radiological parameters, an appreciable number of endoscopies should be avoided **[2]**.

The purpose of this study was to determine to what extent serum serotonin level an effect on the prediction of both oesophagal and gastric fundal varices has.

In the current study, serum serotonin levels showed a highly statistically significant increase in patients' group than the control group, with the higher level was in cirrhotic patients with OV and fundal varices followed by cirrhotic with OV, cirrhotic without OV and the lowest level was in control group. On the same hand Ćulafić et al., **[15]** and Rudić et al., **[16]** reported that serotonin level was higher in liver cirrhosis patients than in controls.

On the other hand, a study was done by Yeoh et al., **[17]** founded that the whole-blood serotonin levels were significantly lower in patients with cirrhosis than in the age-matched controls, with insignificant correlation between these levels and the severity of cirrhosis. But in the same study, the serum serotonin levels (an indication of the active form of serotonin) was significantly higher in cirrhotic patients than in the controls.

In this work, we found that level of serum serotonin was higher in grade IV oesophagal varices (53.94±9.1ng/ml) than grade III oesophagal varices (31.4±23.3ng/ml) and grade (I-II) (29.02±7.05 ng/ml), these results were agreed with the results of Abdelkader et al., **[18]** who found a highly significant stepwise progressive increase in the free serotonin level through grades of OV.

In the present study, there was a significant positive correlation between serum serotonin level and serum creatinine level, presence and grading of oesophagal varices and presence of fundal varices, this was agreed with results of the study done by Hammam et al., **[19]** in which they concluded that serum serotonin level is significantly correlated to the grade of esophageal varices in patients with viral hepatitis-related cirrhosis.

But this result disagreed with the result of Rudić et al., **[16]** who found that no significant correlation between the serotonin concentration and the size of esophageal varices (rs=–0.217, $p>0.05$). However, the correlation of plasma serotonin concentration and gastric fundal varices was highly significant (rs=–0.601, $p<0.01$), this may be due to the difference in the number of patients and the aetiology of cirrhosis as this study include 33 cirrhotic patient and the majority of them were alcoholics.

In the present work, there was a significant negative correlation between serum serotonin level and the platelet count which is one of the main stores of serotonin. This result agreed with Abdelkader et al., **[18]** in which there is a significant negative correlation between platelet count and serum serotonin level (r=–0.316, p=0.05), and this result disagreed with that had been found by Rudić et al., **[16]** in which, there was no significant correlation between serum serotonin level and the platelet count, this may be due to difference in

race of patients and the aetiology of cirrhosis as this study was conducted on patients from the Clinical Center of Serbia the majority of them were alcoholics.

In the present work, serum serotonin level at cutoff value 79.1ng/ml had a sensitivity of 100% and a specificity of 96.6% and AUC=0.99 to predict patients with OV and patients had both OV and fundal varices and this can be explaned by the presents of oesophageo-gastric collaterlas in those patients that may help serotenin after disturbed metabolism to by pass the liver to systemic circulation and this will cause very high increase in its level according to the degree of these collaterals. So, the plasma serotonin level could be used as a non-invasive predictive markerfor the presence or absence of gastro-esophageal varices, that was agreed with Rudić et al., **[16]** and Sieg et al., **[20]** who concluded that free serotonin is significant in pathogenesis of portal hypertension especially in development of fundal varices, indicating the clinical value of sertonergic receptor blockers as ketanserin and ritanserin in the lowering of portal hypertension in patients with liver cirrhosis.

In the present work, serum serotonin level at cut-off value 32.2ng/ml had moderate sensitivity 72% and specificity 60% to predict OV in cirrhotic patients and that coincided with the study of Abdelkader et al., **[18]** who found that serotonin level at cutoff value of 58ng/ml can be used to differentiate between cirrhotic patients with and without OV with 80% sensitivity, 86.7% specificity.

In the present study, serum serotonin level is considered bad marker to differentiate the grade of OV as its level at a cutoff value of 28.4ng/ml had a sensitivity of 55% and a specificity of 25% with AUC=0.27 in the prediction of OV grades, and that agreed with Rudić et al., **[16]** who concluded that serotonin concentration can´t predict size of OV.

In Conclusion:

serum serotonin level could be used as a non-invasive independent predictor for the presence of gastro-oesophagealvarices, which may help in reducing unnecessary endoscopies, but it could not discriminate between the grades of oesophagealvarices. Further studies are recommended to study the role of serum serotonin in the pathogenesis of portal hypertensive gastropathy.

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الآهمية التشخصية لمستويات السيروتونين بمصل الدم فى التنبؤ بوجود دوالى المرئ والمعدة فى مرضى التحجر الكبدى

مقدمة البحث: من المعروف آن السيروتونين هو آحد الموصلات العصبية التى تستطيع تنظيم العديد من الوظائف الحيوية للكبد.

الهدف من البحث: هو تحديد دور السيروتونين بمصل الدم كدلالة غير واخذة (تداخلية) فى التنبؤ بوجود دوالى مرئ ومعدة فى مرضى التحجر الكبدى.

طريقة البحث: إشتملت هذه الدراسة على (٧٠) مريض مصابين بالتحجر الكبدى بسبب عدوى الإلتهاب الكبدى الفيروسى "سى"، و (١٥) شخص من الآصحاء كمجموعة ضابطة وتم تقسيم المرضى طبقاً لما وجد فى المنظار العلوى على المرئ والمعدة إلى ٣ مجموعات:

- مجموعة (آ): إشتملت على (٣٠) مريض بالتحجر الكبدى ليس لديهم دوالى بالمرئ آو المعدة.
- مجموعة (ب): إشتملت على (٢٩) مريض بالتحجر الكبدى ولديهم دوالى مرئ فقط.
- مجموعة (ج): إشتملت على (١١) مريض بالتحجر الكبدى ولديهم دوالى بالمرئ والمعدة.

وقد تم آخذ التاريخ المرضى والفحص الإكلينيكى والإختبارات المعملية الروتينية لكل المرضى بالإضافة إلى قياس مستوى السيروتونين بمصل الدم بإستخدام الإليزا تكنيك.

نتائج البحث: لوحظ زيادة تدريجية فى متوسط مستوى السيروتونين بمصل الدم إلى آن وصل آعلى مستوى فى مرضى دوالى المرئ والمعدة (٨.٥١±٩٤.٠٤ نانوجرام/مل)، يليه مرضى دوالى المرئ فقط (١٨.٣٨±٣٩.٢ نانوجرام/مل) وكان مستوى المجموعتين آعلى من مجموعة المرضى بدون دوالى المرئ، كما وجدت الدراسة علاقة طردية ذات دلالة إحصائية بين مستوى السيروتونين بمصل الدم ومستوى الكرياتين، وجود دوالى بالمرئ ويناسب آيضاً مع درجتها ووجود دوالى بالمعدة، كما وجد آن مستوى السيروتونين بمصل الدم عند (٣٢.٢ نانوجرام/مل) له درجة حساسية تصل إلى ٧.٢٪ ودرجة تخصصية تصل إلى ٦٠٪ فى التنبؤ بوجود دوالى مرئ فى مرضى التحجر الكبدى ولكن عند مستوى (٢٨.٤ نانوجوام/مل) له درجة حساسية قليلة تصل إلى ٥٥٪ ودرجة تخصصية تصل إلى ٢٥٪ فى تمييز درجات الدوالى بينما عند مستوى (٧٩.١ نانوجرام/مل) تصل حساسيته إلى ١٠٠٪ وتخصصية إلى ٩٦.٦٪ فى تشخيص المرضى المصابين بدوالى المرئ والمعدة.

خلاصة البحث: مستويات السيروتونين بمصل الدم يمكن إستخدامها كدلالة غير واخذة (تداخلية) لوجود دوالى المرئ والمعدة ولكنها لا تستطيع التمييز بين الدرجات المختلفة من دوالى المرئ.