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Could serum serotonin be used as a marker for portal vein invasion in patients with hepatocellular carcinoma?

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***Abstract*---**Introduction: Hepatocellular carcinoma represents the sixth and the fourth cause of cancer in the world and Egypt, respectively. In Egypt, HCC mortality and morbidity is high. Serotonin is a precious neurotransmitter and vascular viable molecule. Serotonin plays an important role in hepatocytes mitosis and tumor genesis leading to hepatocellular carcinoma. Aim of Work: To investigate if serum serotonin can be used as a marker for portal vein invasion in patient with hepatocellular carcinoma. Methods: Cross-sectionla analytic study was performed in Suez Canal University Hospitals. The study included 90 participants; 10 normal healthy control individuals and 80 chronic liver disease patients divided into four groups (20 cirrhotic; 20 early HCC; 20 advanced HCC and 20 ablated HCC). All study groups were subjected to the following; history, clinical examination, and investigations including hematological, biochemical, serum Alpha fetoprotein and Serotonin levels) with pelviabdominal ultrasound and Triphasic computerized tomography. Results: Portal Vein Thrombosis (PVT), abnormal liver function tests, and AFP were positively correlate with serum serotonin level. In comparison between study groups, mean serum serotonin level was (117±84, 693±65,1613±37) for patients with normal, dilated, and portal vein invasion respectively with a statistically significant difference (p value <0.001). Conclusion: Serum serotonin can be used as a marker for portal vein invasion in patient with hepatocellular carcinoma.

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***Keywords*---**HCC; hepatocellular carcinoma, AFP; alpha fetoprotein, serum serotonin.

Introduction

Hepatocellular carcinoma represents the sixth obvious cause of cancer **(1)** and the fourth cause of death from cancer **(2)** in the world**,** accounting for 4.7% of all cancers in 2018. HCC is higher in males than in females two to three times. HCC in males is the fifth mostly diagnosed malignancy and the second most prevalent cause of mortality. In females, HCC represents the ninth mostly diagnosed malignancy and the sixth major cause of mortality **(3)**.

In Egypt, hepatocellular carcinoma represents the fourth prevalent malignancy and the most prevalent cause of malignancy related mortality and morbidity **(4).** The incidence of hepatic malignancies were about 11.75% of all gastrointestinal organs malignancies and 1.68% of the total malignancies. HCC represents the main complication of cirrhosis in Egypt due to infection with hepatitis B virus (HBV) and HCV as primary serious factors of cirrhosis progression in screening programs and diagnostic tools **(5).**

The diagnosis of HCC is done by hepatic imaging tests such as abdominal ultrasound and triple phase CT scan in mix with the measurement of serum markers such as alpha-fetoprotein (AFP) but this test had a sensitivity of 39–65%, a specificity of 76–94% in the occurrence of HCC **(6).**

There is an obvious progress in HCC treatment over the last 10 years, with progress in both technology and selection of patients. Available therapeutic options can be included into curative and non curative interventions. Curative therapies conclude surgical resection, hepatic transplantation (LT) and ablative techniques such as thermal and radiofrequency damage. Each of these approaches represent the chance of long-term response and improve chance for alive **(7)**.

Serotonin is known as 5-hydroxytryptamine (5-HT), a biogenic amine that roles as a legend for a large family of 5- HT receptors. The majority of serotonin in the body (90%) is synthesized by enterochromaffin cells of the gastrointestinal tract, where it ordinates intestinal motility **(8).** Serotonin is represented to have a precious role in neurotransmission within the central nervous system and the autonomic nervous system. According to hepatic role, it was discovered that serotonin has the potency to ordinate hepatic blood at both the portal and sinusoidal levels **(9).**

Serotonin has important effect in angiogenesis, hepatocytes mitosis, portal invasion and liver regeneration. Recently, many studies declared the role of serotonin in the tumor growth in different cancers, including HCC **(10)**. Serotonin initiate hepatocellular carcinoma proliferation, invasion and metastasis via regulating Yap expression in vitro and in vivo. Therefore, 5-HT and Yap may be prognostic indicators for HCC patients in the future **(11)**.

So, This study was done to investigate the ability of using serum serotonin as a marker for portal vein invasion in patient with hepatocellular carcinoma.

Study design and subjects:

The study is Cross-sectional analytic study conducted in Internal Medicine and hepatocellular carcinoma Outpatient clinic in Suez Canal university hospital on 90 subjects classified into five groups:

1) Twenty cirrhotic patients.

2) Twenty early HCC patients defined according Barcelona Clinic Liver cancer (BCLC stages 0-A).

3) Twenty advanced HCC patients (BCLC stages B-C).

4) Twenty ablated HCC patients after six months of intervention.

5) Ten healthy subjects as control group.

Inclusion criteria

1- Subjects of both sex male and female

2- More than 18 years old.

3- Patients with liver cirrhosis diagnosed by abdominal ultrasound and laboratory profile.

4- Patients with hepatocellular carcinoma diagnosed by computed tomography (CT) and serum AFP.

5- Patients with ablated heptocellular carcinoma after six months of intervention.

Exclusion criteria

1- Patients with active gastrointestinal bleeding.

2- Patients with recent infection as spontaneous bacterial peritonitis.

3- Patients with neurotic psychiatric disorders other than hepatic encephalopathy.

4- persons with impaired kidney function.

5- Patients without HCC ablated after six months of intervention.

Methods:

Study included 90 subjects matched to the inclusion criteria each one was subjected to:

1-History taking:

- Sex and age.
- Symptoms of cirrhotic liver (history of bleeding, encephalopathy, and previous drugs).

2-Full examination:

- Signs of (jaundice, ascites, spleenomegaly, lower limb edema, astrexis or any disturbance in the level of consciousness).

3-Laboratory tests*:*

- Hematological (CBC).
- Renal function test (serum Creatinine).
- Hepatic function tests (liver enzymes, bilirubin (total & direct), albumin, PT, INR).
- Hepatic virology (HCV-antibody & HBs-antigen).

4-Special tests:

- Assessment of serotonin in blood with immune enzymatic assays by **(Human Serotonin ELISA Kit from Bioassay Technology Laboratory, Catalog Number: E1128Hu).**
- Measurement of serum alpha fetoprotein.
- Pelviabdominal ultrasound.
- Tri-phases CT pelviabdominal to identify HCC nodules and portal vein invasion.

Statistical analysis

Data was entered to the computer using the predictive Analytics Software. Continuous variables were expressed as mean and standard deviation, and comparisons were performed using ANOVA test, and post-hoc test. Categorical variables were expressed as numbers and percent, and comparisons were performed using chi square test. Categorical variables were expressed as numbers and percent, and comparisons were performed using chi square test. Associations

were tested using Pearson Correlation Coefficient. P value less than 0.05 was considered significant.

Results

Table 1
Comparison of different background characteristics among study groups

	Cirrhosis n = 20	**Early HCC n = 20**	**Advanced HCC n = 20**	**Ablated HCC n = 20**	**Total n = 80**	**P value**
Age (years)						
Mean ± SD	57 ± 11	54 ± 11	59 ± 9	58 ± 8	57 ± 11	0.5
Gender						
Males	10 (50)	11 (55)	14 (70)	12 (60)	47(58.7)	0.6
Females	10 (50)	9 (45)	6 (30)	8 (40)	33 (41.3)	
Virology						
Negative	0 (0)	1 (5)	1 (5)	1 (5)	3 (3.8)	0.7
HCV +	16 (80)	18 (90)	17 (85)	17 (85)	68 (85)	
HBV +	4 (20)	1 (5)	2 (10)	2 (10)	9 (11.2)	
Child-Pugh						
A	5 (25)	12 (60)	3 (15)	18 (90)	38 (47.5)	<0.001
B	9 (45)	8 (40)	4 (20)	2 (10)	23 (28.7)	
C	6 (30)	0 (0)	13 (65)	0 (0)	19 (23.8)	

Table 1: showed that the mean age of diseased groups were 57 ± 11 years and the number of male participants was higher than females (58.7% versus 41.3%) however that no statistical difference between study groups according age or sex. Regarding to virological affection, Most of patients were positive for HCV (85%). Regarding to Child-Pugh score, most of the patients met criteria of Child-Pugh A (47.5%), followed by Child-Pugh B (28.7%), and the least frequent score was C (23.8%)**.**

Table 2
Comparison of hematological background among study groups.

	Cirrhosis n = 20	**Early HCC n = 20**	**Advanced HCC n = 20**	**Ablated HCC n = 20**	**P value**
Hb (g/dL)	10.7±1.5	11.6±1.8	9.2±2	12.7±1.5	0.003
TLC(x10^3\ul)	4.9±2.1	5.3±2.4	5.0±2.3	5.6±1.6	0.7
PLT (x10^3\ul)	103±51	131±90	106±62	126±61	0.4
PT (INR)	17.1±3.4	14.9±1.7	19.1±4.4	14.1±2	0.001

Concerning the hematological data of study groups, the mean hemoglobin level and prothrombin time were significant statistically between groups (p value < 0.003).

Table 3
Comparison of liver and kidney functions among study groups.

	Cirrhosis n = 20	**HCC n = 20**	**Advanced HCC n = 20**	**Ablated HCC n = 20**	**P value**
AST(IU/L)	69±35	61±39	83±50	56±36	0.1
ALT(IU/L)	60±26	48±33	73±52	45±27	0.08
T. Bilirubin(mg/dL)	2.1±1.2	1.3±0.9	2.7±2.1	0.9±0.4	<0.001
D. Bilirubin(mg/dL)	1.7±1.1	0.7±0.7	1.9±1.7	0.3±0.3	<0.001
Albumin(g/dL)	3.1±0.7	3.6±0.7	2.9±0.7	3.8±0.5	<0.001
Creatinine(mg/dL)	0.85±0.19	0.82±0.18	1.05±0.34	0.80±0.21	0.5

Concerning liver function tests, The mean bilirubin (total & direct) and serum albumin were statistically significant. Concerning kidney function test, the mean creatinine level was within normal range among all groups without statistically significant difference .

Table 4
Correlation between serotonin level and different laboratory and Portal vein invasion and thrombosis (PVT)

Variables	**R**	**P value**
Negative correlation		
TLC	-0.1	0.07
HB	-0.2	0.01
PLT	-0.2	0.04
Albumin	-0.4	<0.001
Positive correlations		
PVT	0.2	0.003
Child-Pugh score	0.3	<0.001
AST	0.3	0. 01
ALT	0.3	<0.001
PT	0.4	<0.001
T. Bilirubin	0.4	<0.001
D. Bilirubin	0.4	<0.001
AFP	0.5	<0.001

Serotonin is negatively correlated with total leukocytes count (TLC), hemoglobin (HB), platelets count (PLT) and albumin level. Abnormal liver function tests showed positive correlation with high serotonin level, in addition to Portal Vein invasion (PVT) and AFP that positively correlate with serum serotonin level **.**

Table 5
Correlation between serum serotonin level and portal vein invasion and thrombosis (PVT)

	Serotonin (ng/ml)			
	Mean ± SD	**Range**		P
Portal Vein				
Normal	117±84	101	: 325	<0.001
Dilated	693±65	310	: 1446	
Invasion Thrombosis)(	1613±37	1248	: 4542	

In comparison between study groups for portal vein; The mean serum serotonin level was (117±84, 693±65,1613±37) for patients with normal, dilated, and portal vein invasion respectively with a statistically significant difference (p value <0.001).

Discussion

A cross-sectional analytic study that was achieved aiming to detect possibility of using serotonin as an indicator of HCC ablation, diagnosis and prognosis.

In this study, the mean age of diseased groups were 57 ± 11 years, number of participants, males were higher than females (58.7% versus 41.3%) as, **Mamdouh et. al., (2019)**, Reported that males were higher than females (75% versus 25%) **(12)**. Most of patients were positive for HCV (85%), (11.2%) positive for HBV and only (3.8%) negative virology **(12)**. This is due to increased HCV infection in Egypt leading to cirrhosis and HCC **(5).** Concerning the hematological data of study, Only hemoglobin level was statistically significant between groups. The mean prothrombin time tended to be prolonged in all groups especially cirrhotic and advanced HCC patients with (p value < 0.001) among groups due to decreased synthetic function of the liver.

Concerning liver function tests, the mean levels of ALT, AST and total & direct bilirubin were increased in patient with cirrhosis and advanced HCC groups with significance only with bilirubin, while the serum albumin was decreased in cirrhotic and advanced HCC groups with (p value < 0.001). Concerning kidney function test, the mean creatinine level was within normal range among all groups without statistically significant difference. **Mamdouh et. al., (2019)**, reported that the median hemoglobin level, total leukocyte count and platelet count were lower in late HCC group with statistically significant difference

(12).Concerning liver function tests, the median levels of bilirubin and prothrombin time were increased in cirrhotic and late HCC groups, while the serum albumin was significantly decreased in cirrhotic and late HCC groups.

We detected in our study a positive correlation between serotonin and AFP (P value < 0.001, r = 0.5) and that agreed with **Elshayed et. al., 2016**, who found a significant positive correlation between serum AFP and serum serotonin (P value < 0.001, r = 0.95)(P value < 0.001, r = 0.8) **(13).** Serum serotonin was significantly correlated positively with portal vein invasion and this point to the role of serotonin in HCC prognosis and vascular invasion as published by **Elshayed et. al., 2016**, who found that serum serotonin positively correlated with portal vein diameter with statistically significant correlation **(13)** and in agreement with **lui et. al., 2018,** who demonstrated that serotonin played an essential role in proliferation, invasion and metastasis through promotion of Yap expression **(11).**

Conclusion

- Serum serotonin can be used as a marker for portal vein invasion in patient with hepatocellular carcinoma.

- Liver functions (except for serum albumin) and portal vein thrombosis had positive correlation with serum serotonin, which points to the value of serum serotonin as a prognostic HCC marker.

Recommendations

- larger-scale studies are recommended to determine that Serum serotonin can be used as a marker for portal vein invasion in patient with hepatocellular carcinoma.

- Serum serotonin can be used as prognostic marker for hepatocellular carcinoma.

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