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Original article

Assessment of Annexin A2 as A Marker for Diagnosis of Hepatocellular Carcinoma in Compensated and Decompensated Hepatitis C Virus Treated Patients

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Abstract

Background: In the entire world, hepatocellular carcinoma (HCC) is considered as one of the most prevalent cancers. For earlier identification to enhance the clinical outcomes of HCC patients, more sensitive and specific indicators are required. **Aim:** To identify HCC, it is necessary to assess the annexin A2 levels in both compensated and decompensated HCV-treated patients. **Methods:** At the time of diagnosis and before starting treatment, blood specimens from 40 HCC individuals were taken and isolated plasma specimens were maintained at -80 °C until ANXA2 assays. The human ANXA2 enzyme-linked immunosorbent test (ELISA) kit was used to collect blood specimens from forty individuals with CHC but no HCC at the same

duration as the blood specimens from HCC patients. Anti-ANXA2 antibodies were utilized as identification antibodies. **Results:** With a p-value of <0.001, the ANXA2 level sensitivity and specificity test demonstrated a statistically significant difference in the identification of HCC cases in both compensated and decompensate populations. In comparison to the decompensated group, the ANXA2 level's sensitivity in diagnosing HCC patients was 90% in the compensated status. Regarding AFP and ANXA2 levels, there was a statistically significant distinction (p <0.001) between the two study groups, with a greater mean among the HCC group**. Conclusion:** The combination of annexin A2 and AFP significantly boosts the diagnostic capability of this promising HCC diagnostic marker. Its serum concentration can be used as an effective, non-invasive tumour marker for HCC identification.

1. Introduction:

Worldwide, hepatocellular carcinoma (HCC) constitutes one of the most prevalent cancers. According to an investigation conducted by Egypt's National Population-Based Cancer Registry Program, liver cancer was the most common type of cancer among Egyptian men (33%), second only to breast cancer among women (13.5%), and first overall (23.8%). Hepatitis C virus (HCV) dissemination was followed by the growth of liver cancer (1). Egypt has the biggest worldwide incidence of hepatitis C virus (HCV) infection (2). Hepatocellular carcinoma (HCC) and cirrhosis are both caused by chronic hepatitis C (CHC), which is a significant risk factor (3).

For early detection to enhance the medical outcomes of HCC patients, more sensitive and specific indicators are required. A number of human cancers exhibit an overexpression of annexin A2 (ANXA2), an inducible, calcium-dependent phospholipid-binding protein. An appealing putative

receptor for enhanced plasmin production on the surface of tumour cells is annexin A2. In healthy liver tissues and tissues affected by chronic hepatitis, ANXA2 is essentially undetectable (4).

Consequently, the current study's objective was to assess the amount of annexin A2 in compensated and decompensated HCV-treated patients in order to diagnosis HCC because it is a useful diagnostic and predictive marker for early HCC in patients with chronic hepatitis C.

2. Patients and Methods:

Patient:

80 patients were included in this study and divided into two groups.

Group (1): 40 HCV-treated patients, 20 of whom had compensated liver cirrhosis and 20 did not, were free of HCC.

Group (2): 40 HCV patients with HCC, 20 of whom had compensated liver cirrhosis and 20 did not.

Between November 2021 and May 2022, patients were chosen from the internal medicine department of the Beni-Suef university hospital according on the preceding inclusion and exclusion criteria:

Inclusion criteria:

The investigation involved both males and females who were older than 18. Participants in the research were HCV-treated people without HCC, Individuals with HCC who have HCV, including those with compensated and decompensated liver cirrhosis, were also included.

Exclusion criteria:

Patients under the age of 18, those with other cancers, those who had viral hepatitis rather than HCV, those with a history of autoimmune illnesses, and those with other significant comorbidities were all excluded from the study.

Ethical consideration:

Patients received comprehensive information from researchers regarding the trial and the marker used. All parties involved provided their written, informed consent. Beni-Suef University's ethical committee gave its approval. At the study sites, all research-related data had been safely kept. All participant data was kept in secured filing cabinets in restricted areas. In order to protect confidentiality, data gathered from respondents could only be tracked by a coded identifier code. All records including names or additional

personal characteristics were kept apart from study records designated by code number, including locator forms and informed consent forms. Password-protected access procedures were used to protect all local databases.

Methods:

Careful history-taking, clinical examination and routine laboratory testing, including CBC, kidney functioning tests (urea and creatinine), liver function tests (ALT, AST, albumin, bilirubin), INR, HCV Ab, HBs Ag, and Alpha feto-protein, were all performed on the patients. Special emphasis was placed on the manifestations of hepatitis C and hepatocellular carcinoma, as well as family history. ANXA2 serum levels were assessed using the ELISA (enzyme-linked immuneosorbent assay) method.

Radiological investigation had been performed using abdominal ultrasound and triphasic computerized tomography of the liver if hepatic focal lesions detected.

Statistical Analysis:

Data was collected, double-entered into Microsoft Access, and then coded to facilitate data processing. SPSS software version 22 operating on Windows 7 was used for the analysis of statistics (SPSS Inc., Chicago, IL, USA). For a basic descriptive assessment, percentages and numbers had been utilized for qualitative data, arithmetic means had been used to measure central tendency, and standard deviations had been used for calculating the variance of parametric quantitative data. Independent sample T test was utilized to contrast quantitative data between two different groups. With the help of the benferroni Post-HOC assessment, To assess the quantitative variations between more than two independent variations in quantitative data, a one-way ANOVA test was used. Kruskal-Wallis analysis was used for evaluating multiple independent groups. The Mann-Whitney test is used for comparing two independent groups. In order to compare two or more qualitative classifications, the chi square test was used. To examine the relationship between parameters, the bivariate Pearson correlation test was used. Applying the "Receiver Operating Characteristic" (ROC) curve, tests were performed to determine the sensitivity and specificity of novel tests. Statistical significance was defined as a P-value of 0.05 or less.

3. Results:

Table 1 showed that compensated HCV cases had a statistically significant lower

mean age than decompensated HCV and compensated HCC cases. However, there was no disparity in the sex distribution across the four groups, with a p-value of >0.05 (figure 1).

Table 1: Comparisons of demographic characteristics in different study groups.

Variables	HCV		HCC		P-value
	Compensated	Decompensate	Compensated	Decompensate	
	Mean±SD	Mean ±SD	Mean ±SD	Mean ±SD	
Age(years)	49.5±12	64±9.6	62.6±9.8	64.2±6.7	<0.001 a,c* 0.9b,d
Sex	No. (%)	No. (%)	No. (%)	No. (%)	
Male	13(65%)	12(60%)	15(75%)	18(90%)	0.2
Female	7(35%)	8(40%)	5(25%)	2(10%)	

a: significance difference between comp. & decomp HCV groups

b: significance difference between comp. & decomp HCC groups

c: significance difference between comp. HCV& HCC groups

d: significance difference between decomp HCV&HCC groups

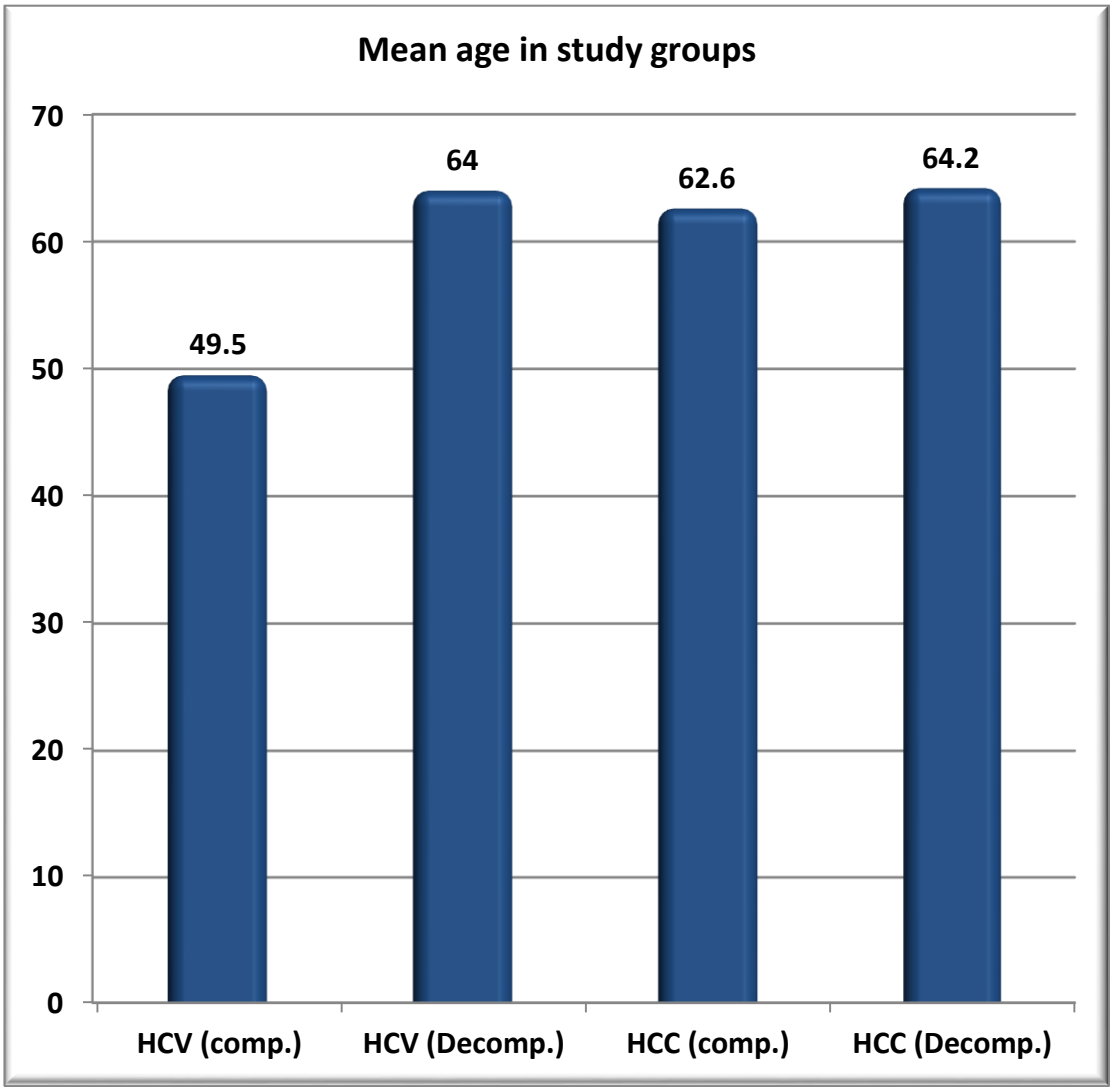

Figure (1) Mean Age In Different Groups

Regarding haemoglobin level, PLT, PC, INR, and liver function tests (ALT, AST, bilirubin, and albumin levels), Table 2 demonstrated a statistically significant variance (p-value <0.05) across the four groups being investigated. On the other hand, testing for renal function and TLC with p-values >0.05 revealed no distinction between the four groups.

Table 2: Correlations between laboratory tests conducted among the study groups.

Variables	HCV		HCC		P-value
	Compensated	Decompensate	Compensated	Decompensate	
	Mean±SD	Mean ±SD	Mean ±SD	Mean ±SD	
CBC					
Hg	**10.8±0.67**	**9.4±1.6**	**9.5±2.6**	**11.9±1.7**	**0.08a <0.001b,d*0.1c**
PLT	**200.8±29.1**	**146.3±50.7**	**163.5±69.8**	**163.5±69.8**	**0.02a* 0.9b 0.3c 0.9d**
TLC	**7.1±1.8**	**7.2±2.4**	**6.5±1.9**	**7.5±1.5**	**0.9 a,b,c,d**
PC	**80.9±9.9**	**60.7±8.9**	**68.8±13.3**	**73.1±14.1**	**<0.001*a 0.9 b,d 0.01*c**
INR	**1.13±0.10**	**3.4±1.2**	**2.9±1.2**	**3.6±1.1**	**<0.001*a,c 0.3b 0.9d**
Liver function tests					
ALT	**22.3±7.6**	**131.8±62.5**	**92.8±59.7**	**48.5±39.3**	**<0.001*a,c,d 0.02*b**
AST	**19.9±6.7**	**107±49.8**	**87.7±51.2**	**63.1±41.1**	**<0.001*a,c 0.4b 0.007*d**
Bilirubin	**0.86±0.33**	**5.7±3.7**	**2.1±1.4**	**1.6±1.8**	**<0.001*a,d 0.9b 0.4c**
Albumin	**4.1±0.54**	**2.8±0.64**	**2.9±0.43**	**3.2±0.62**	**<0.001*a,c 0.4b 0.1d**
Kidney function tests					
Createine	**0.97±0.22**	**0.89±0.22**	**0.93±0.23**	**0.97±0.22**	**0.9 a,b,c,d**
Urea	**29.9±9.7**	**28.7±6.6**	**29.7±6.1**	**29.3±5.9**	**0.9 a,b,c,d**

a: significance difference between comp. & decomp HCV groups

b: significance difference between comp. & decomp HCC groups

c: significance difference between comp. HCV& HCC groups

d: significance difference between decomp HCV&HCC groups

Table 3 revealed that the AFP and ANXA2 values between the four study groups differed statistically and significantly (p-value < 0.05), with the decompensated HCC group having an elevated mean (figures 2 and 3).

Table (3): Comparisons between tumour markers across various study groups.

Variables	HCV		HCC		P-value
	Compensated	Decompensate	Compensated	Decompensate	
	Mean±SD	Mean ±SD	Mean ±SD	Mean ±SD	
AFP	4.1±3.5	4.9±4.8	43.1±21.4	72.4±45.9	0.9a 0.003*b <0.001*c,d
ANXA2	3.9±1.2	3.8±1.2	5.8±1.8	5.7±1.4	0.9 a,b <0.001*c,d

a: significance difference between comp. & decomp HCV groups

b: significance difference between comp. & decomp HCC groups

c: significance difference between comp. HCV& HCC groups

d: significance difference between decomp HCV&HCC groups

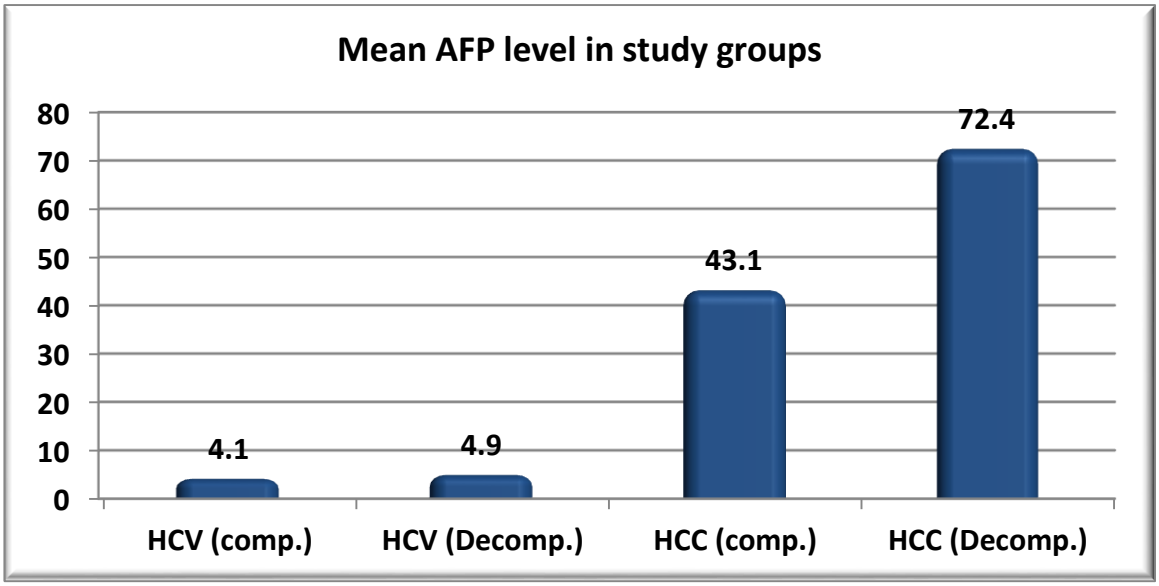

Figure (2) Mean AFP level in study groups

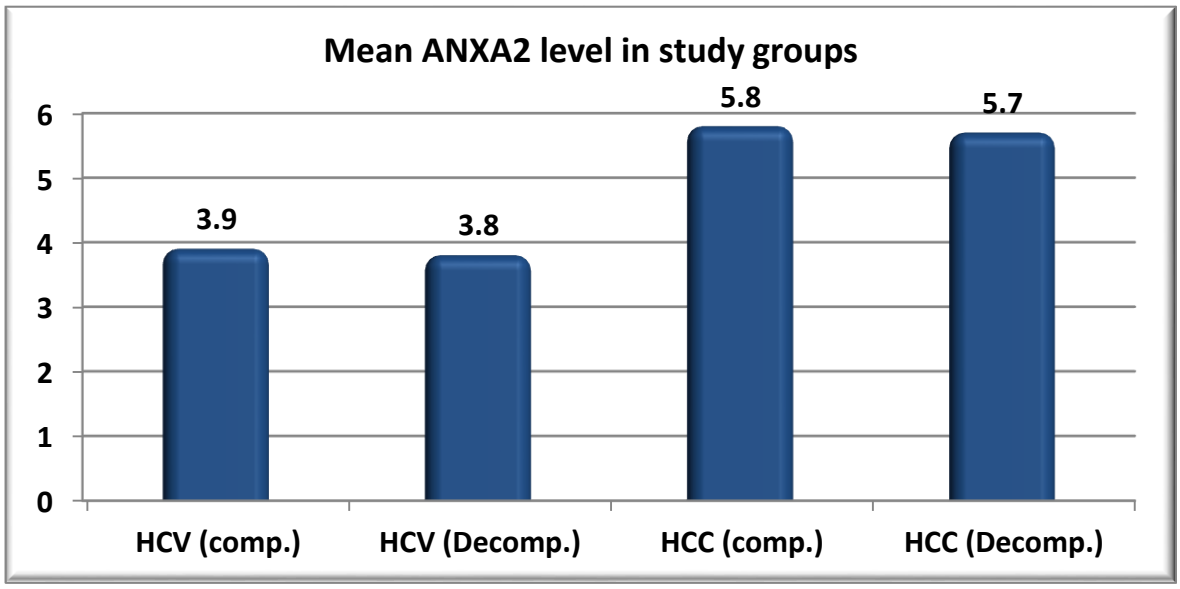

Figure (3) Mean ANXA2 level in study groups

Table 4 shows that there was a statistically significant distinction in AFP and ANXA2 levels between the two groups under consideration, with a greater mean among the HCC group (p-value <0.001).

Table (4): Tumour marker comparisons across various examination groups.

Variables	HCV		HCC		P-value
	Mean±SD	Median (range)	Mean±SD	Median (range)	
AFP	4.5±4.2	2.6 (0.2-18.9)	57.8±38.3	52.1 (11-192.8)	<0.001
ANXA2	3.9±1.2	4 (0.3-6.2)	5.8±1.6	5.8 (1.6-10.3)	<0.001

Table 5 demonstrated that there was no statistically significant variance in the virology assessment between the four groups under investigation with a p-value of >0.05.

Table (5): comparisons of virology findings across various study groups.

Variables	HCV		HCC		P-value
	Compensated	Decompensate	Compensated	Decompensate	
	No. (%)	No. (%)	No. (%)	No. (%)	
HCV Ab					
Negative	**0(0%)**	**0(0%)**	**0(0%)**	**0(0%)**	**----**
Positive	**20(100%)**	**20(100%)**	**20(100%)**	**20(100%)**	
HB s Ag					
Negative	**20(100%)**	**20(100%)**	**20(100%)**	**20(100%)**	**----**
Positive	**0(0%)**	**0(0%)**	**0(0%)**	**0(0%)**	

a: significance difference between comp. & decomp HCV groups

b: significance difference between comp. & decomp HCC groups

c: significance difference between comp. HCV& HCC groups

d: significance difference between decomp HCV&HCC groups

Regarding the existence of ascitis and splenomegaly, with a p-value below 0.05, table 6 demonstrated a statistically significant variation among the four groups under study indicating a larger percentage among decompansated patients in both the HCV and HCC groups (figures 4 and 5).

Table (6): Comparisons of clinical findings in different study groups.

Variables	HCV		HCC		P-value
	Compensated	Decompensate	Compensated	Decompensate	
	No. (%)	No. (%)	No. (%)	No. (%)	
Ascitis					
No	**20(100%)**	**6(30%)**	**10(50%)**	**6(30%)**	**<0.001*a 0.2b 0.003*c 0.9d**
Yes	**0(0%)**	**14(70%)**	**10(50%)**	**14(70%)**	
Splenomegaly					
No	**20(100%)**	**5(25%)**	**13(65%)**	**4(20%)**	**<0.001*a 0.004*b 0.003*c 0.7d**
Yes	**0(0%)**	**15(75%)**	**7(35%)**	**16(80%)**	

a: significance difference between comp. & decomp HCV groups

b: significance difference between comp. & decomp HCC groups

c: significance difference between comp. HCV& HCC groups

d: significance difference between decomp HCV&HCC groups

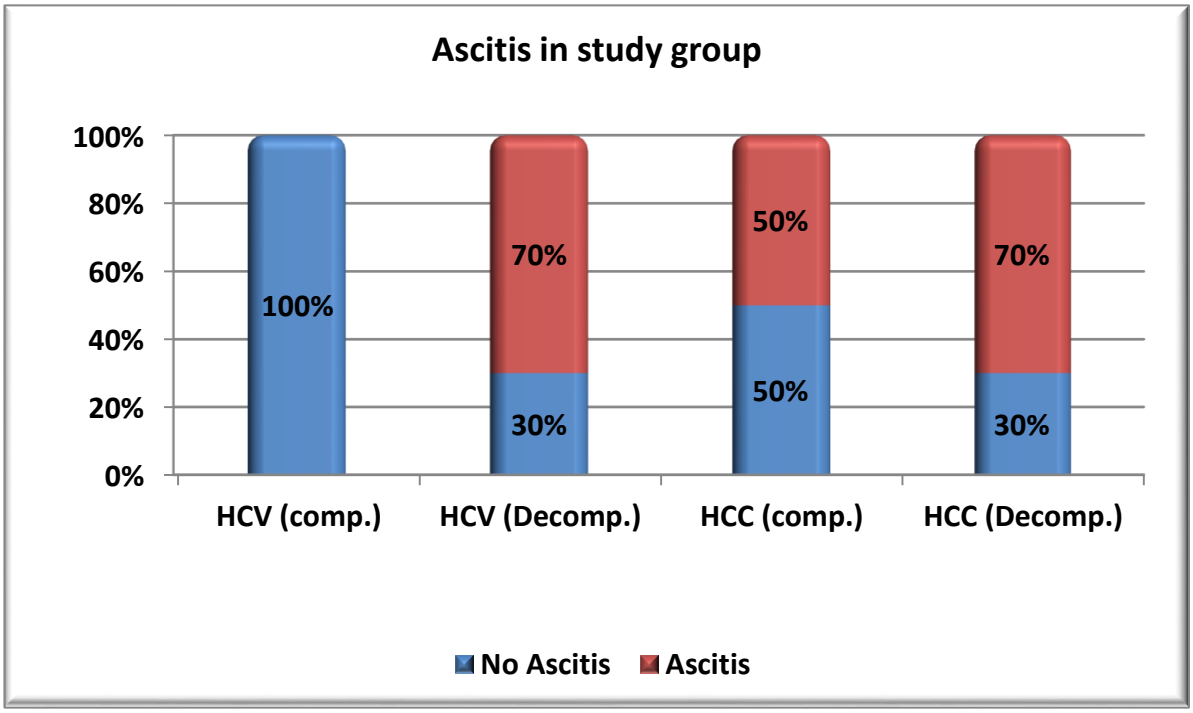

Figure (4) Ascites in study groups

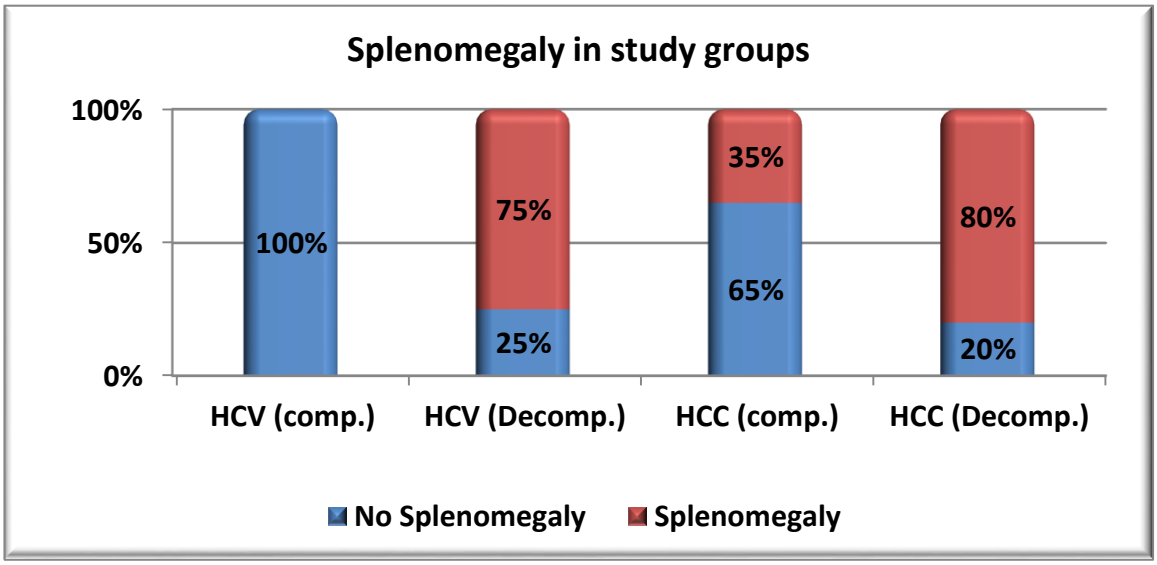

Figure (5) Splenomegaly in study groups

According to Table 7, there was no statistically significant variation between the HCC groups (compensated and decompansated) in terms of tumour size, tumour number, or portal vein thrombosis.

Table (7): Comparisons of tumor characteristics in different HCC groups.

Variables	HCC		P-value
	Compensated	Decompensate	
	No. (%)	No. (%)	
Tumor size			
<2cm	13(65%)	9(45%)	0.3
>2cm	7(35%)	11(55%)	
Tumor number			
Single	12(80%)	10(50%)	0.8
Multiple	8(40%)	10(50%)	
Portal vein thrombosis			
No thrombosis	15(75%)	13(65%)	0.7
Thrombosis	5(25%)	7(35%)	

Table 8 showed a statistically significant positive connection between ANXA2 level and TLC with p-value <0.05, indicating that a rise in TLC will be associated with a higher levels in ANXA2 content. However, there was no statistically significant link between ANXA2 level and all other HCV case investigations with p-value >0.05.

Table (8): Correlation between ANXA2 with routine investigations among HCV cases.

Variables	ANXA2(ng/ml)		
	r	P-value	Sig.
Age (years)	0.12	0.5	NS
Hg	0.005	0.9	NS
PLT	0.21	0.2	NS
TLC	0.35	0.02*	S
PC	0.04	0.8	NS
INR	0.03	0.8	NS
ALT	0.08	0.6	NS
AST	0.06	0.7	NS
Bilirubin	0.09	0.6	NS
Albumin	-0.17	0.3	NS
Createine	-0.15	0.3	NS
Urea	-0.29	0.07	NS
AFP	-0.09	0.5	NS

significance difference with p-value <0.05

Table 9 demonstrated that no statistically significant relationship existed between the ANXA2 value and any of the other HCC cases examined with a p-value greater than 0.05.

Table (9): Correlation between ANXA2 with routine investigations among HCC cases.

Variables	ANXA2(ng/ml)		
	R	P-value	Sig.
Age (years)	-0.14	0.4	NS
Hg	0.20	0.2	NS
PLT	0.17	0.3	NS
TLC	-0.17	0.3	NS
PC	-0.03	0.8	NS
INR	-0.06	0.7	NS
ALT	-0.17	0.3	NS
AST	-0.14	0.4	NS
Bilirubin	-0.16	0.3	NS
Albumin	0.17	0.3	NS
Createine	-0.15	0.4	NS
Urea	-0.08	0.6	NS
AFP	-0.19	0.2	NS

Sensitivity and specificity tests for the ANXA2 level showed that neither research group (HCV or HCC) could reliably diagnose the condition of decomposition (figures 6 and 7).

Table (10): Sensitivity and specificity of ANXA2 in diagnosis of decompensate degree of both HCV and HCC cases.

Decompensate cases	Sensitivity	Specificity	Accuracy	Cut off point	P-value
HCV	**80%**	**30%**	**50.7%**	**4.75**	**0.9**
HCC	**75%**	**35%**	**53%**	**5.15**	**0.7**

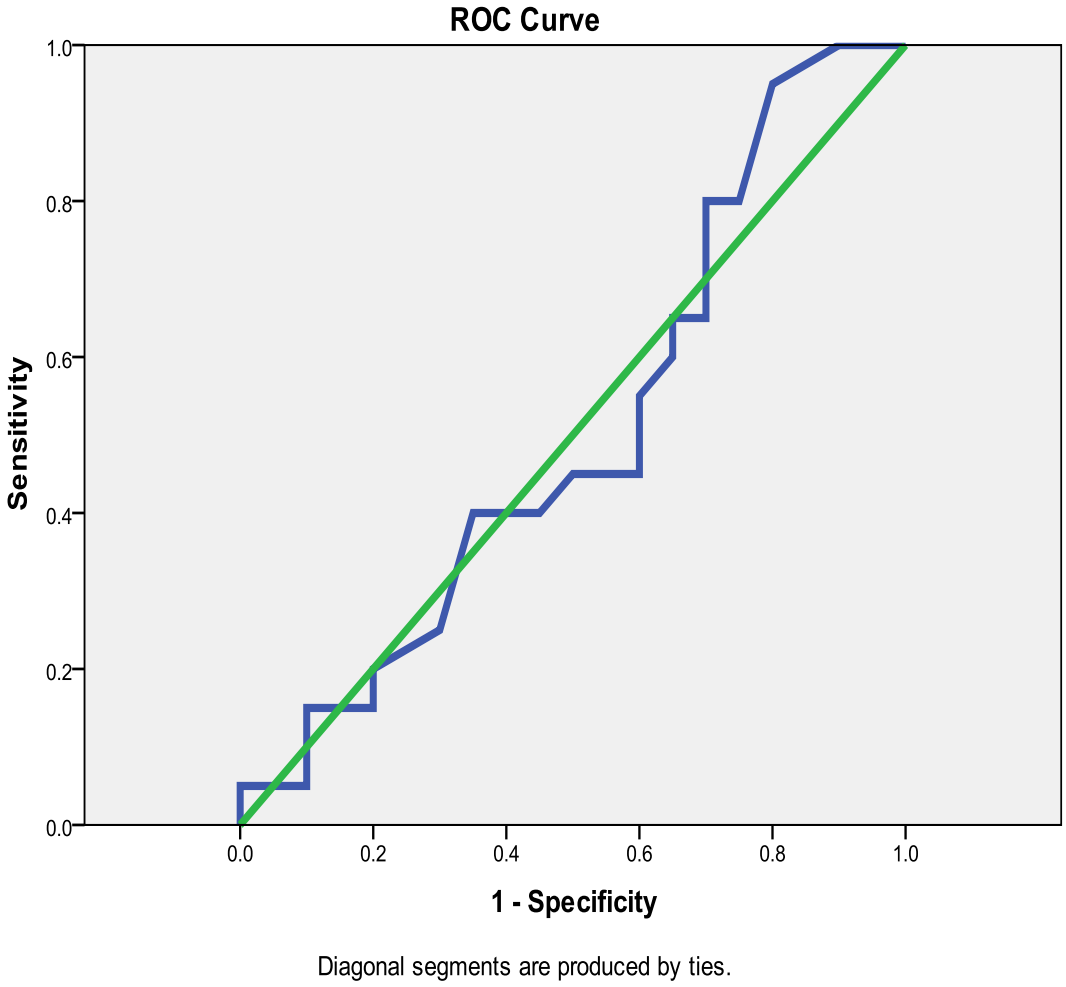

Figure (6): ROC curve for ANXA2 level in diagnosis of decompensated condition cases among (HCV)

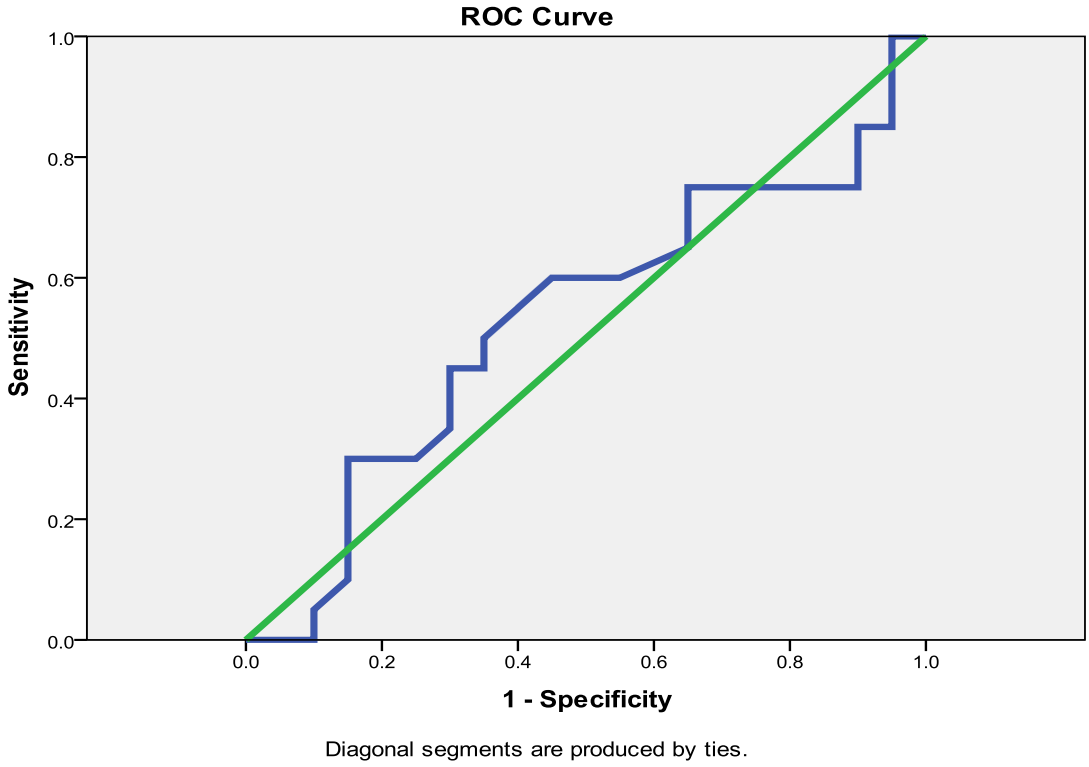

Figure (7): ROC curve for ANXA2 level in diagnosis of decompensated condition cases among (HCC)

With a p-value of < 0.001, the ANXA2 level sensitivity and specificity test demonstrated a significant value in the identification of HCC cases in both compensated and decompensate cohorts. In comparison to the decompensated group, the ANXA2 level's sensitivity in diagnosing HCC patients was 90% in the compensated condition (figures 8 and 9).

Table (11): Sensitivity and specificity of ANXA2 in diagnosis of HCC cases in compensated and decompensate group

HCC cases	Sensitivity	Specificity	Accuracy	Cut off point	P-value
Compensated	**90%**	**70%**	**83.1%**	**4.65**	**<0.001***
Decompensate	**80%**	**65%**	**85.6%**	**4.35**	**<0.001***

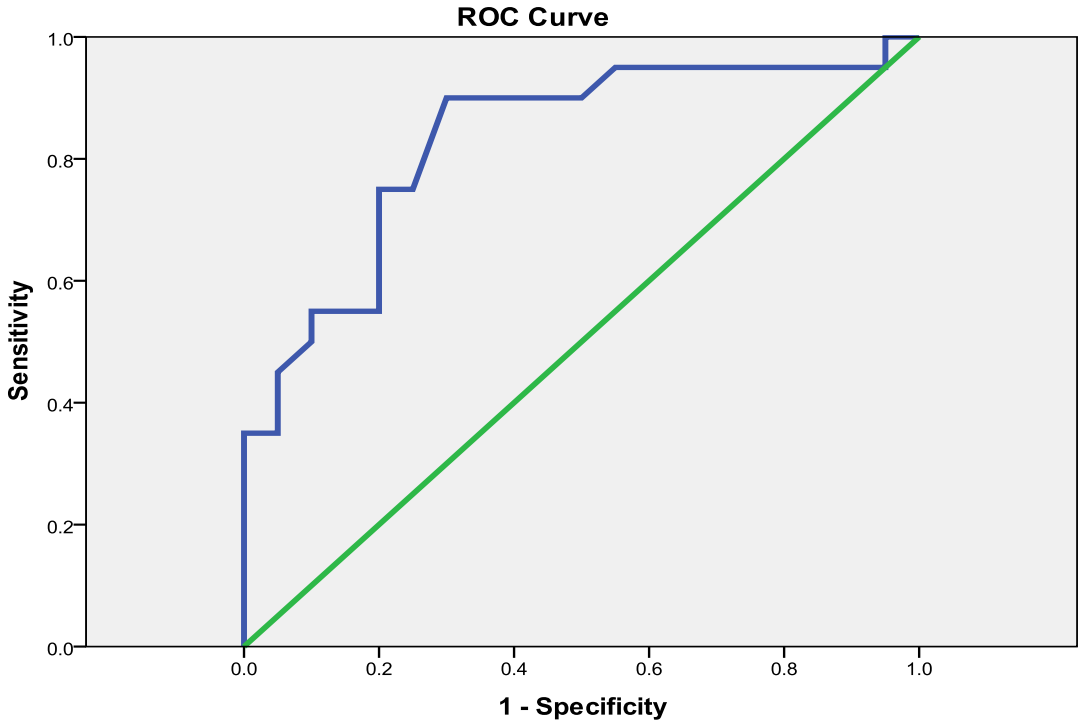

Figure (8): ROC curve for ANXA2 level in diagnosis of HCC cases among compensated condition (HCV& HCC)

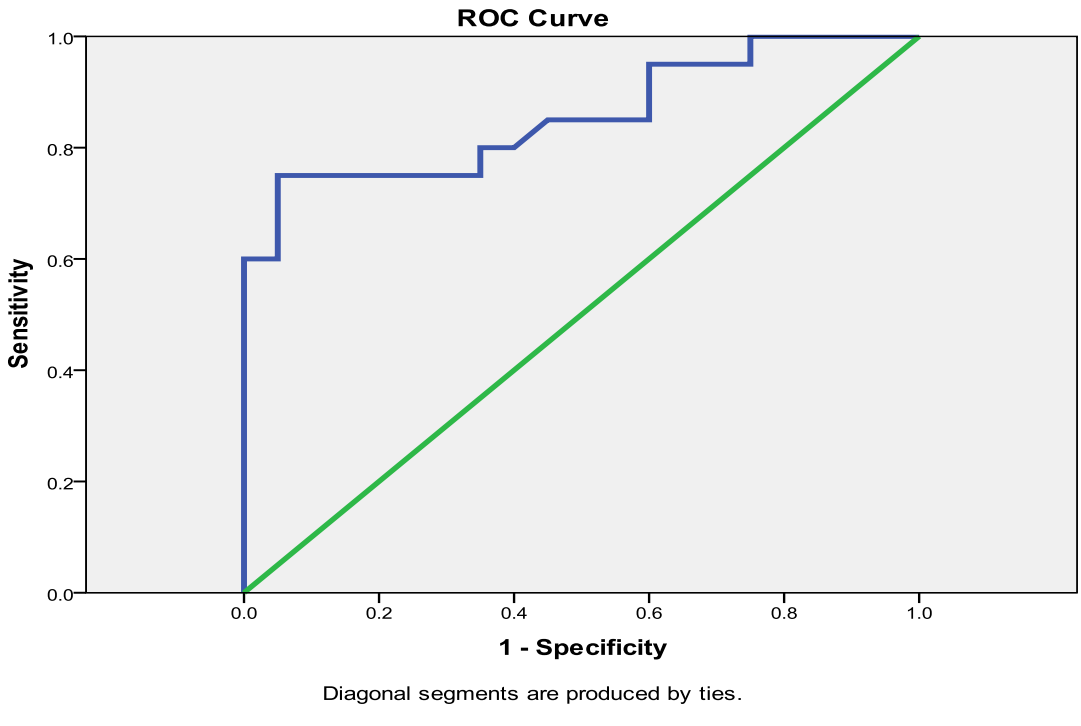

Figure (9): ROC curve for ANXA2 level in diagnosis of HCC cases among decompensated condition (HCV& HCC)

4. Discussion:

Hepatocellular carcinoma (HCC) is the most common type of primary hepatic cancer (5) and the sixth most frequent malignancy in terms of cancer-related deaths globally (6).

It has traditionally been referred to as a tumour with a dismal outlook. Numerous studies connected this poor prognosis to the delayed diagnosis and the absence of an ideal diagnostic indicator with sufficient diagnostic fidelity. Numerous laboratory and imaging modalities are part of the diagnostic toolbox for HCC.

The most efficient technology is typically thought to be serum marker detection because it is more practical and affordable. Nevertheless, their diagnostic effectiveness is insufficient. The annexin family, which includes Annexin A2 (ANXA2), has been shown to play significant roles in the development of cancer, involving signal transduction, angiogenesis, apoptosis, tumour invasion, and metastasis. This 36-kDa calcium-dependent phospholipid-binding protein is present on the surface of the majority of eukaryotic cells.

It affects a number of biological techniques, such as phospholipase A2 regulation, Ca2+-dependent exocytosis, anti-inflammatory actions, and immunological reactions (7).

Breast, liver, prostate, and pancreatic cancers, among others, have been shown to express ANXA2 more frequently than healthy tissues (8, 9).

In terms of HCC, the advanced stage of liver cirrhosis, which is regarded as a precancerous step, could be connected with an alteration in the tumour microenvironment and the spread of tumour cells, which could end up in the hepatocyte malignant transformation and the growth of HCC (ref).

Additionally, by causing the conversion of plasminogen to plasmin, which activates matrix metalloproteinase and causes the breakdown of extracellular matrix elements, ANXA2 promotes tumour metastasis. It does this by binding with plasminogen and tissue plasminogen activator on the cell surface (ref).

Therefore, the purpose of our study was to assess annexin A2's potential as a diagnostic serological marker for the diagnosis of HCC. Additionally, in order to potentially increase diagnostic accuracy via increased sensitivity and specificity, we correlated it with another well-recognized HCC marker (alpha fetoprotein).

In our cross-sectional observational study, individuals with either compensated, decompensated liver cirrhosis or HCV were enrolled. Both compensated and decompensated liver cirrhosis is present in HCC patients.

When 40 HCC patients were diagnosed and before starting treatment, blood samples were taken, until ANXA2 assays could be performed, separated plasma samples were kept at -80 °C. Blood samples from 40 people with CHC but no HCC were obtained using the human ANXA2 enzyme-linked immunological sorbent test (ELISA) kit over the same time period. The technology used in this kit was sandwich ELISA.

Our study's findings suggest a statistically significant positive association between ANXA2 level and TLC, with a p-value of 0.05 indicating that a rise in TLC will be associated with an increase in ANXA2 level. Yet, no statistically significant variance was found. The lack of any statistically significant association between the level of ANXA2 and all other HCV investigation results with p-values >0.05 demonstrated that there is also no such link between the level of ANXA2 and all other HCC investigation results.

With a p-value of <0.001, the sensitivity and specificity test for the ANXA2 value demonstrated that there is a substantial value in the identification of HCC patients in both the compensated and the decompensate groups. In comparison to the decompensated group, the ANXA2 level's sensitivity in diagnosing HCC patients was 90% in the compensated condition.

Previous findings are consistent with this research (10, 11) however, contrary to individuals with child's grades A and B, individuals in the child's C group had higher levels of annexin A2. and revealed no significant difference between the different prognostic factors in the HCC group annexin.

There was a statistically significant difference (p-value <0.001) between the two study groups in terms of AFP and ANXA2 levels, with a higher mean among the HCC group, and that is consistent with the research carried out by Sun et al. (2013) (4) which demonstrated that annexin A2 and AFP together have a sensitivity and specificity of 76 and 80.5%, respectively. Another study were done by Zhang et al. (2012) (12) stated that the diagnostic effectiveness (96.5%) and the negative predictive value (96.6%) for HCC were both significantly

increased when serum ANXA2 and AFP were detected together.

These findings support the management of HCC diagnosis with ANXA2 and AFP.

Last but not least, our findings indicated that annexin A2 is a promising diagnostic marker for HCC, and that its combination with AFP significantly boosts the diagnostic power. Its serum concentration can be used as an effective, non-invasive tumour marker for HCC identification.

5. Conclusions:

The annexin family, which includes Annexin A2 (ANXA2), has been shown to play significant roles in the development of cancer, encompassing signal transduction, angiogenesis, apoptosis, tumour invasion, and metastasis. Contrary to normal or cirrhotic tissue, HCC has higher levels of ANXA2 expression. The diagnostic power of Annexin A2, a promising HCC diagnostic marker, when combined with AFP is significantly increased. Its serum concentration can be used as an effective, non-invasive tumour marker for HCC identification.

Recommendations:

Future prospective studies on larger population should be performed to reach a higher diagnostic accuracy. Annexin A2 should also be evaluated in different populations to assess it accuracy. Further assessment of other biomarkers is recommended to reach higher specificity in assessment of HCC patients. Combination of two or more of non-invasive biomarkers is recommended to reach higher accuracy in assessment of HCC.

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