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# COBALAMIN (VITAMIN B12) AS A TUMOR MARKER FOR DETECTION OF HCC AMONG EGYPTIAN PATIENTS WITH POST HEPATITIC CIRRHOSIS

By

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## ABSTRACT

**Background:** Worldwide hepatocellular carcinoma (HCC) is one of the most common forms of cancer and is the third leading cause of cancer related death with chronic hepatitis C virus (HCV) infection being a major risk factor. Although alfa-fetoprotein (AFP) is a commonly used tumor marker in the detection of HCC, it has low sensitivity reaching 40% in detection of small HCC. Cobalamin acts as co enzyme for physiologically important functions in humans and stored in liver.

**Objective:** To evaluate the significance of serum cobalamin level as a new diagnostic marker for HCC in patients with post hepatitic liver cirrhosis.

**Patients and methods:** This cross sectional observational study 80 persons were recruited from the department of Gastroenterology and Hepatology in Al-Azhar University Hospitals, Hepatology department in Ahmed Maher teaching Hospital and EL Menshawy Tanta hospital, and divided into two equal groups: Group I patients with Post hepatitis cirrhosis with HCC, and Group II patients with Post hepatitis cirrhosis patients without HCC. The study was carried out in the period of December 2018 to February 2020.

**Results:** Cobalamin and AFP levels were significant higher in group I than group II and there was positive correlation between coblamin levels and AFP levels in group I. At cut of value cobalamin levels ≥ 840 pg/ml is the best as a marker of HCC with the sensitivity is 62.5%, specificity 80%, positive predictive value 75.8%, negative predictive value 68.1%, AUC=0.725, and p> 0.001. the ROC curve showed that AFP was superior to cobalamin in diagnosing HCC with higher sensitivity, specificity, and the area under the curve (AUC) While Combined usage of cobalamin and AFP revealed higher diagnostic performance in HCC diagnosis than using one of each markers alone with sensitivity 77.5%, specificity 92%, AUC (0.8760) positive predictive value 91.2, and negative predictive value 80.4%.

**Conclusion:** Combined cobalamin and AFP revealed higher diagnostic performance in HCC diagnosis than using one of each marker alone with sensitivity 77.5%, specificity 92%, AUC (0.8760), positive predictive value 91.2, and negative predictive value 80.4%.

**Keywords:** Cobalamin (Vitamin B12), HCC, AFP, HCV.

## INTRODUCTION

Liver cancer is the fifth most common cancer and the second most frequent cause of cancer-related death globally *(Akinyemiju et al., 2017).* Hepatotropic viruses such as HBV, HCV, and hepatitis D virus (HDV) have a strong association with development of HCC; thus, the worldwide distribution of HCC mirrors the distributions of such viral infections *(Green et al., 2017).*

It has a poor prognosis after discovery, which is usually at a late stage of disease. This had been strongly linked to the hepatitis C virus epidemic that affected around 10-15% of the Egyptian population during the last 3 decades, and was reported as the highest prevalence of HCV in the world *(Elghazaly et al., 2018).*

Less common causes of HCC include hereditary hemochromatosis, alpha1-antitrypsin deficiency, autoimmune hepatitis, and Wilson's disease. Most of these risk factors lead to the formation and progression of cirrhosis, which is present in 80 to 90% of patients with HCC *(El-Serag, 2011).*

Ultrasound examination of the liver and detection of AFP level in serum are commonly used to screen for HCC. Although detection of AFP level is easy and less expensive, but it shows less sensitivity, since elevation in AFP level is common in patients with chronic liver disease, pregnancy and germ cell tumors. AFP titers also rise with flares of active hepatitis, and may be persistently elevated in patients with cirrhosis. Ultrasound is better, but is more expensive, operator dependent and less reliable in the presence of cirrhosis. Thus, new markers with high sensitivity and specificity are required *(Zakhary et al., 2013).*

Current treatment strategies, such as liver transplantation, surgical resection or regional therapy for advanced HCC, are unsatisfactory. Chemotherapy is commonly used for the treatment of various malignancies. However, systemic cytotoxic chemotherapeutic agents have not significantly improved the survival of HCC patients because of the resistance of HCC to anticancer drugs. Tumor recurrence after curative liver resection remains high, and most patients die within several months of diagnosis *(Jiang et al., 2014).*

Vitamin B12 (Cobalamin) is a coenzyme for two physiologically important functions in humans: 1-The synthesis of methionine, and 2- the conversion of methylmalonic acid to succinic acid. Also, the synthesis of methionine requires methylcobalamin. Therefore all living cells require vitamin B12, rapidly dividing tumor cells have a highly increased need for this vitamin *(Hamid et al., 2013).*

Three proteins such as intrinsic factor (IF), transcobalamin (TC), and haptocorrin (HC) are involved in the uptake and transport of cobalamin. Vitamin B12 is known to accumulate at high levels in the liver. Therefore, the concentration of vitamin B12 in blood rises in the presence of acute or chronic liver disease. Therefore when the liver is injured, stored vitamin B12 leaks out into the blood, which causes a severe B12-deficit in the liver. Most of the studies indicate that patients with chronic liver disease, cirrhosis, HCC have higher level of serum cobalamin, HC ve TC II than

normal patients. These high level results can be considered as marker of tumor and also can be directly associated with progression of disease or size of tumor *(Öksüz et al., 2016).*

**The aim of this study was to** evaluate the possibility of using vitamin B12 (cobalamin) as a new tumor marker for HCC in patients with post hepatitis cirrhosis.

## PATIENTS AND METHODS

This cross sectional observational study, it was carried out on 80 patients presented with post-hepatitis cirrhosis with or without HCC. All patients were selected from the inpatient wards, outpatient clinics of internal medicine departments of Al-Hussein, Al-Menshawy and Ahmed Maher hospitals. The study was carried out in the period of December 2018 to February 2020.

They were divided into two equal groups: Group I: Post hepatitis cirrhosis patients with HCC diagnosed by history, clinical examination, abdominal ultrasonography, elevated AFP levels and evidence of focal hepatic lesions suggestive for HCC by tri-phasic CT, Group II Post hepatitis cirrhosis patients without HCC.

**Ethical considerations:** The nature of the study was explained to all participants and/ or their relatives and verbal consents were obtained.

**Inclusion criteria:** Eighty Egyptian adult (n=80) patients, with post Hepatitis cirrhosis with or without HCC were selected for inclusion. The diagnosis of post hepatitis cirrhosis (including the etiology) was made by history, clinical examination, laboratory investigations, and abdominal ultrasonography.

**Exclusion criteria:**

1. Patients on vitamin B12 Therapy.
2. Patients with any active neoplastic disorder other than HCC.
3. Patients who underwent any surgical resection, ethanol injection or chemo-embolization had been performed for management HCC.
4. Patients with HCC who were receiving chemotherapy.
5. Patients with other chronic medical diseases, those with active or severe infections and those with cerebrovascular stroke.

**All patients underwent to:**

**A. Full history taking:** with special stress on history of chronic liver disease (its cause and duration if known)

**B. Full clinical examination:** including general and abdominal examination to assess manifestations of cirrhosis and its severity.

**C. Laboratory investigations:**

- Method of sample collection: venous blood samples were taken from each patient at the morning following an overnight fasting. Furtherly, Samples were centrifuged to obtain the sera and were furtherly preserved at -20°C for subsequent biochemical analysis.
- All biochemical laboratory tests were including: Liver function tests, liver enzymes, total and direct bilirubin, renal function tests, complete blood count, glucose homeostatic

parameters, viral markers by third generation ELISA technique to determine the underlying viral etiology of post hepatitis cirrhosis including: HbsAg and anti-HCV antibodies, quantitative determination of serum Alpha-fetoprotein levels, the normal reference range (10-20ng/ml). The cut of value of serum AFP that was suspicious of malignancy was > 400 ng /ml (reference), and quantitative determination of serum B12 by ELISA. The normal reference range was (200-800) pg/ml.

**D. Radiological investigations:**

1. Pelvi-abdominal ultrasonography: Ultrasound examination was used for diagnosis of cirrhosis and its complications as well as detection of HCC.
2. Triphasic CT abdomen: to confirm HCC nature of hepatic focal lesion among patients of group I as well as to exclude HCC focal lesions among patients of group II. Accordingly, the diagnosis of HCC was confirmed if the hepatic focal lesion showed rapid enhancement in the arterial-phase with rapid washout in the venous and delayed phases *(Marrero et al., 2018).*

The numbers, size, and sites of the lesion were furtherly determined.

**Statistical analysis:**

Statistical analysis was performed using SPSS software version 23 for Windows (SPSS Inc., Chicago, IL, USA). Normally distributed data were exemplified in the form of Mean ± SD and the particular groups were compared using Student's t-test. Moreover, categorical variables were elucidated as number and percentage and compared using Fisher Exact test or Chi-square test. Correlation analysis was performed using Pearson's correlation coefficient for continuous normally distributed variables, while Spearman's rank correlation was used for other variables. Z-test was used to compare the statistical significance of the difference between two independent correlation coefficients to determine the strength of correlation in either group. Receiver operating characteristic (ROC) curve and area under the ROC curve (AUC) were used to assess the diagnostic ability of biomarkers. The optimal cuts off points were calculated to maximize sensitivity and specificity. All tests were considered significant when $P < 0.05$.

## RESULTS

The ages of patients included in group I ranged between 39 to 71years with a Mean ± SD of (56.88 ± 7.67) years, of them 28 subjects (70 %) were males & the remaining 12 ones (30 %) were females while the ages of patients included in group II ranged between 37 to 76 years with a Mean ± SD of (54.20 ± 6.68) years, of them 29 subjects (72.5 %) were males and the remaining 11 ones (27.5 %) were females.

There were no statistically significant difference between the studied groups regarding their age, sex and viral etiology distribution **(Tables 1)**.

**Table (1): Age, sex and viral infection distribution &differences within the studied groups**

| Variables \ Groups | Group (I) (N=40) | Group (II) (N=40) | P-value |
|---|---|---|---|
| **Age (year)**<br>Mean ± SD<br>Range | <br>56.88±7.67<br>39-71 | <br>54.2±6.68<br>37-76 | 0.112 |
| | **No. (%)** | **No. (%)** | |
| **Sex:**<br>Males<br>Females | <br>28 (70%)<br>12 (30%) | <br>29 (72.5%)<br>11 (27.5%) | 0.80 |
| **Viral Infection**:<br>HCV<br>HBV | <br>35 (87.5%)<br>5 (12.5%) | <br>36 (90%)<br>4 (10%) | 0.125 |

The levels of cobalamin (Pg/mL) were significantly higher in group I than in group II with (mean ± SD) levels (1089.5 ± 455.3) VS (726.82 ± 198.6) (pg/ml) respectively. The levels of AFP (ng/ml) were significantly higher in group I than in group II with (mean ± SD) levels (717.7 ± 1092.1) VS (19.63 ± 23.6) (ng/ml) respectively **(Tables 2)**.

**Table (2): Comparison between both groups regarding cobalamin and AFP levels**

| Variables \ Groups | | Group (I) (N=40) | Group (II) (N=40) | P value |
|---|---|---|---|---|
| **AFP (ng/mL)** | **(Mean ± SD)** | **717.7 ± 1092.1** | **19.63 ± 23.6** | **<0.0005** |
| **Cobalamin (pg/mL)** | **(Mean ± SD)** | **1089.5 ± 455.3** | **726.82 ± 198.6** | **<0.0005** |

Among the patients of group I; the subjects with single HFL detected by ultrasound were 12 (30%) while the patients with 2 HFLs were 19 (47.5%) and Patients with 3 HFLs were 9 (22%).

By Tri-phasic CT, the patients with single HFL were 10 (25%) while the patients with 2 HFLs were 21 (52.5%) and Patients with 3 HFLs were 9 (22%).

There was no statistically significant difference between the ultrasound vs triphasic CT modalities in detection of the exact number of HFLs among patients of group I.

The (Mean ± SD) size of the largest dimension of the single (or the largest one if multiple HFLs) was (4.42 ± 2.15) cm by ultrasound compared to that was detected by tri- phasic CT (4.58 ± 2.23) cm with no statistically significant difference between the aforementioned radiological modalities **(Tables 3)**.

**Table (3): Numbers and dimensions of HFLs detected in subjects of group I by triphasic CT and ultrasound**

| No. of (HFLs) | One HFL | | Two HFLS | | Three HFLS | | P-value |
|---|---|---|---|---|---|---|---|
| | U/S | CT | U/S | CT | U/S | CT | |
| No. (%) | 12 (30%) | 10 (25%) | 19 (47.5%) | 21 (52.5%) | 9 (22%) | 9 (22.5%) | 0.51 |
| Size of HFLs (Mean ± SD) | By (U/S) | | By (tri-phasic CT) | | | | 0.741 |
| | 4.42 ± 2.15 | | 4.58 ± 2.23 | | | | |

ROC curves for serum cobalamin as well as AFP were drawn to show the cut-off levels with the corresponding diagnostic performance parameters for prediction the diagnosis of HCC among the patients of studied groups.

Serum AFP had a significant diagnostic performance in differentiating study groups ($p < 0.001$) with AUC = 0.807. Similarly, Serum cobalamin had a significant diagnostic performance in differentiating study groups ($p < 0.001$) with AUC = 0.725.

At a cutoff point ≥ 35.5 ng/ml for AFP, the sensitivity was 67.5%, specificity 92.5%, positive predictive value 90%, and negative predictive value 74% in detecting HCC among the patients of studied groups.

At a cutoff point ≥840 pg/ml for cobalamin, the sensitivity was 62.5%, specificity 80%, positive predictive value 75.8%, and negative predictive value was 68.1% in detecting HCC among the patients of studied groups.

Combining both cobalamin and AFP at the aforementioned cutoffs resulted in improvement in the diagnostic performance in differentiating HCC among the studied groups compared to either one of them alone [(AUC increased to be 0.867) with further increase in sensitivity to 77.5%, however the specificity was the same as was for AFP (92.5%) **(Table 4)**.

**Table (4): Diagnostic characteristics of cobalamin and AFP as a diagnostic markers for HCC.**

| | Serum AFP (cutoff ≥35.5 ng/ml) | Serum cobalamin (cutoff ≥ 840 (pg/ml)) | Combined serum cobalamin and AFP |
|---|---|---|---|
| **Characters** | **Value** | **Value** | **Value** |
| **Area under the curve (AUC)** | 0.807 | 0.725 | 0.876 |
| **Sensitivity** | 67.5 % | 62.5% | 77.5% |
| **Specificity** | 92.5% | 80.0% | 92.5% |
| **Positive Predictive value (PPV)** | 90% | 75.8% | 91.2% |
| **Negative Predictive value (NPV)** | 74% | 68.1% | 80.4% |
| **Positive likelihood ratio (LR+)** | 9 | 3.13 | 10.3 |
| **Negative likelihood ratio (LR-)** | 0.35 | 0.47 | 0.24 |

Correlations Between the serum AFP and cobalamin levels With the Size of largest HFLs and Number of HFLs detected by tri-phasic CT in group I.

There was statistically significant positive correlation between both serum AFP and cobalamin levels among patients of group I.

There was no statistically significant correlation between either serum cobalamin or AFP levels with the numbers of HFLs as well as the sizes of the largest HFLs detected by tri-phasic CT among patients of group I **(Table 5)**.

**Table (5): Correlations Between the serum AFP and cobalamin levels With the Size of largest HFLs and Number of HFLs detected by tri-phasic CT in group I**

| VARAIBLE | S. Cobalamin levels (pg/ml) | | S. AFP levels (ng/ml) | |
|---|---|---|---|---|
| | r | p-value | r | P-value |
| S. Cobalamin levels (pg/ml) | | | 0.37 | 0.019 |
| Size (HFLs) | 0.133 | 0.414 | 0.172 | 0.288 |
| Number of HFLs | - 0.129 | 0.427 | 0.100 | 0.537 |

## DISCUSSION

The major leading cause for HCC is cirrhosis of the liver which occurring due to many causes. The major known risk factors for HCC can be divided into four categories: viral (chronic hepatitis B and hepatitis C), toxic (alcohol and aflatoxins), metabolic (diabetes and non-alcoholic fatty liver disease, hereditary hemochromatosis), and immune-related (primary biliary cirrhosis and autoimmune hepatitis *(Brouwer-Brolsma et al., 2015).*

In Egypt, HCC incidence has doubled in the past 10 years, which could be attributed to the high prevalence of hepatitis C virus (HCV) and hepatitis B virus (HBV) *(Iyer et al., 2010)* and up to 90% of HCC cases were due to post hepatitis C liver cirrhosis *(Saleh et al., 2012).*

HCC almost always runs a fulminant course and carries an especially grave prognosis *(Kew, 2014)*. SO that, the purpose of surveillance for HCC is to identify tumors early when they might be more amenable to curative therapy and hence decrease HCC-related mortality *(Bruix and Sherman, 2011).*

Unfortunately, HCC surveillance lacks reliable biomarkers. AFP historically has been the most used biomarker but it had the unsatisfactory specificity and sensitivity in screening for HCC *(Allison et al., 2016).* So that, more tumor markers are required for effective early diagnosis of disease and monitoring of the curative effect *(Zhao et al., 2013).*

In the current study, The mean age was (56.88±7.67) years in HCC group which is slightly higher than mean age of cirrhotic group (54.20±6.68 )years and these results showed no significant differences between the studied groups (p-value =0.112).

These results are in agreement with *Mohmad et al. (2010), Atta et al. (2012)* who reported that the mean age among HCC cases was 56 years.

In contrast, *Gupta et al. (2013)* reported an older age with average 61 years and the same happened with *Hafeez*

*et al. (2011)* and *Bhat et al. (2015)* who reported average age of HCC 62 years and 66 years respectively. Such controversy may be due to small number of studied groups or ethnic differences.

In the current study, HCC commonly presented in males more than females (70%, 30%) respectively with male to female ratio 2.66:1 and this was in agreement with *Bartlett et al. (2012)* who reported that men are two to three times higher than women with HCC in most regions. Our result was near to study done by *El-Zayadi et al. (2011)* and revealed that male patients were forming 82.55% while female patients were forming 17.45% among 321 studied HCC patients.

In this study, (87.5%) of HCC and (90%) of cirrhotic groups were HCV-Ab positive. This result was the same result of a study done by *Hafeez et al. (2011)* and near to *Atta et al. (2012), Saleh et al. (2012)* and *El-Zayadi et al. (2011)* who reported that 95%, 87.9%, and 90% of HCC cases were HCV-Ab positive respectively.

Abdominal ultrasonography was done to evaluate the liver status in the studied patients and (100 %) of the patients of HCC and cirrhotic group had sonographic evidence of liver cirrhosis. This agreed with *Bhat et al. (2015)* who reported that cirrhosis is present in the vast majority of patients with HCC and estimated to vary between 90% and 95%.

In the current study the main etiological cause of post hepatitis HCC and post hepatitic cirrhosis was HCV (87.5%,90%) respectively and this agreed with *Shaker et al. (2013)* study that reported that the Underlying HCV related liver disease was responsible for 91% of the cases.

AFP is the most established tumour marker in HCC and the gold standard by which other markers for the disease are judged *(Lopez, 2010)*.

In this study, AFP was significantly higher in Post Hepatitis HCC group than Post Hepatitis Cirrhotic group ($p<0.0001$) with median levels (717.7±1092.1), (19.63±23.6) ng/ml respectively.

This agreed with *El-Tayeh et al. (2012)* which found a significant elevation of serum AFP in HCC patients (558.1 IU/L) than in cirrhotic patients (15.9 IU/L). Also in agreement with *Durazo et al. (2010)* who found the serum level of AFP was significantly higher in HCC patients than non-HCC patients ($P< 0.0001$) and also agreed with *Li et al. (2015)* and *El-Tayeh et al. (2012)*.

Cobalamin was significantly different between both studied groups being higher in post hepatitis HCC group than post hepatitis cirrhotic group ($p<0.0005$) with mean levels (1089.5±455.3), (726.82±198.6)) pg/ml respectively.

These results agree with *Öksüz et al. (2016)* who stated that serum cobalamin level was significantly higher in cancerous cirrhotic HCC group than non-cancerous Cirrhotic group with mean level (1106.2±731.6pg/ml) and (445.8±184.1 pg/ml) ($p<0.001$) but disagree with *Cui et al. (2016)* who noted that there was no significant difference in the mean of plasma vitamin B12 levels between patents with HCC and controls.

These different results might be due to the small sample sizes in the studies, differences in the methods of measuring

vitamin B12 level, differences in ethnicity between the subjects, or differences in tumor stages of HCC.

There is no significant positive correlation between cobalamin level and tumour size (p =0.854, r = 0.030) and this agreed with *Öksüz et al. (2016)* who stated that there is no significant positive correlation between serum cobalamin level and tumour size and disagreed with *Lin et al. (2010)* who noted that Serum VitB12 levels were positively correlated with tumor size (r = 0.630, P = 0.001 in patients with HCC).this may be due to differences in the methods of measuring vitamin B12 level, differences in ethnicity between the subjects.

There was significant positive correlation between cobalamin and AFP (P=0.019, r =0.37) and this was agreed with *Öksüz et al., (2016)* and also agreed with *Lin et al. (2010)* who noted that Serum VitB12 levels were positively correlated with alpha-fetal protein (AFP) levels ( r = 0.623, P = 0.001).

Our study showed that cutoff value for cobalamin ≥ 840 pg/ml is the best as a marker of HCC with the sensitivity is 62.5%, specificity 80%, positive predictive value 75.8%, negative predictive value 68.1%, AUC=0.725, and p> 0.001). While, *Öksüz et al. (2016)* found that that the Sensitivity and specificity of vitamin B12 when AFP as a gold standard serological test was 89.4%and 68.4% respectively.

In such study, at a cutoff point ≥ 35.5 ng/ml for AFP, the sensitivity is 67.50%, specificity 92.5%,, positive predictive value 90%, and negative predictive value 74%. This result was slightly lower than *Li et al. (2015)* who found that at a cutoff value of AFP of ≥ 18.5 ng/ml, the sensitivity is 78.4%, specificity 81.3%, AUC=0.878, and p> 0.0001.

In our study, the ROC curve showed that AFP was superior to cobalamin in diagnosing HCC with higher sensitivity, specificity, and AUC. Combined usage of cobalamin and AFP revealed higher diagnostic performance in HCC diagnosis than using one of each markers alone with sensitivity 77.5%, specificity 92%,AUC (0.8760) positive predictive value 91.2, and negative predictive value 80.4%.

## CONCLUSION

**Cobalamin** is significantly elevated in cancerous post hepatitis cirrhotic HCC group than in non-cancerous post hepatitis cirrhotic group.

Cutoff value for **cobalamin ≥ 840 pg/ml** is the best as a marker of HCC with the sensitivity is 62.5%, specificity 80%, positive predictive value 75.8%, negative predictive value 68.1%, AUC=0.725, and p> 0.001.

**Combined cobalamin and AFP** revealed higher diagnostic performance in HCC diagnosis than using one of each marker alone with sensitivity 77.5%, specificity 92%, AUC (0.8760), positive predictive value 91.2, and negative predictive value 80.4%.

**Cobalamin** has significant positive correlation with AFP but has not significant correlation with HCC size.

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# الكوبالامين (فيتامين ب١٢) كمؤشر للكشف عن سرطان الخلايا الكبدية فى المرضى المصريين بعد تليف الكبد الناتج عن الإلتهاب الكبدي

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**خلفية البحث:** يعد سرطان الخلايا الكبدية من أكثر أنواع السرطانات شيوعاً وثالث سبب للوفيات الناتجه عن الأورام السرطانيه عالمياً حيث تعتبر الإصابه المزمنه بالإلتهاب الكبدى الفيروسى سى من أهم المسببات لسرطان الخلايا الكبدية. وبالرغم من الاستخدام الواسع لتحليل الالفا فيتو بروتين للكشف عن سرطان الخلايا الكبديه ولكن حساسيته تكون منخفضه حيث تصل إلى٤٠٪ فى الكشف عن الأورام صغيره الحجم. يعمل الكوبالامين كإنزيم مساعد لوظائف مهمة من الناحية الفسيولوجية لدى البشر ويتم تخزينه في الكبد.

**الهدف من البحث:** تقييم أهميه مستوى الكوبالامين فى الدم كدلالة تشخيصية حديثة لسرطان الكبد فى مرضى تليف الكبد الناتج عن الالتهاب الكبدى الفيروسى (سى او ب).

**المرضي وطرق البحث:** أجريت هذه الدراسة بمستشفيات جامعة الأزهر وقسم أمراض الكبد بمستشفى أحمد ماهر التعليمي ومستشفى المنشاوي بطنطا، وتم إدراج ثمانون شخصا بالدراسه مقسمين الى مجموعتين متساويتين حيث تتكون المجموعه الأولى من المرضي بسرطان الخلايا الكبدية و التليف الكبدى الناتج عن الاصابه بالفيروس الكبدى (سى او ب)، و المجموعه الثانيه تتكون من المرضي بالتليف الكبدى الناتج عن الإصابه بالفيروس الكبدى (سى او ب) بدون سرطان كمجموعة ضابطة.

**نتـــائج البحـــث:** مســـتويات الكوبـــالامين و الالفـــا فيتـــو بـــروتين كانـــت أعلـــى بشـــكل ملحـــوظ فـــي المجموعـــة الأولـــى مـــن المجموعـــة الثانيـــة وكـــان هنـــاك ارتبـــاط إيجـــابي بـــين مســـتويات الكوبـــالامين ومســـتويات الالفـــا فيتـــو بـــروتين فـــي المجموعـــة الأولـــى. وقـــد أظهـــر منحنـــى الـــروك كيـــرف أن الالفـــا فيتـــو بـــروتين كـــان متفوقًـــا علـــى الكوبـــالامين فـــي تشـــخيص ســـرطان الكبـــد بحساســـية ونوعيـــة أعلـــى بينمـــا أظهـــر الاســـتخدام المشـــترك لكوبـــالامين و الالفـــا فيتـــو بـــروتين أداءً تشخيصـــيًا أعلـــى فـــي تشـــخيص ســـرطان الكبـــد مقارنـــة باســـتخدام كـــل علـــى حـــدة مـــع حساســـية ٧٧.٥٪، وخصوصـــية ٩٢٪، القيمـــة التنبؤيـــة الإيجابيـــة ٩١.٢، والقيمـــة التنبؤيـــة السلبية ٨٠.٤٪.

**الاســـتنتاج:** الكوبـــالامين عنـــد مســـتوى > ٨٤٠ بيكـــوغرام/ مـــل هـــو الأفضـــل كعلامـــة علـــى ســـرطان الكبـــد مـــع حساســـية ٦٢.٥٪، ونوعيـــة ٨٠٪، وقيمـــة تنبؤيـــة إيجابيـــة ٧٥.٨٪، وقيمـــة تنبؤيـــة ســـلبية ٦٨.١٪. إســـتخدام الكوبـــالامين كعلامـــة تشخيصـــية لمـــرض ســـرطان الكبـــد ولا يوجـــد علاقـــه تناســـب طـــردى بـــين مســـتوى الكوبالامين بالدم وحجم وأعداد الأورام السرطانيه بالكبد.

**الكلمـــات الدالـــة:** الكوبـــالامين (فيتـــامين ب ١٢)، الأورام الســـرطانية بالكبـــد، بالفيروس الكبدى (سى او ب).