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# Biochemical Studies of Matrix Metalloproteinase (MMP) and tissue inhibitor of Metalloproteinase (TIMP) as New Biomarkers in HCV - Chronic liver disease

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**Abstract**: The present study aimed to investigate serum levels of Matrix Metalloproteinase (MMP9) and tissue inhibitor of Metalloproteinase (TIMP-1) as new biomarkers in HCV Chronic liver disease. Patients and methods: The study included 35 patients suffering from Chronic liver disease attending at Gastro Entrology Surgical Center (GEC), Mansoura University from 2016 to 2017 and 25 healthy individuals (HI) used as control group ,the studied groups were categorized into 14 patients (9 men and 5women; mean age 53.34±9.46yrs) suffering from HCC associated with HCV infection, 11patients (9 men and 2 women; mean age 52.34±9.14yrs) suffering from LC associated with HCV infection and 10 patients (7 men and 3women; mean age 48.9 ± 12.4yrs) suffering from Chronic Hepatitis (CH). Sera of all individuals were examined for TNF-α, LDH, AFP, ALT, AST, Albumin, T.Bilirubin, GGT, MMP-9 and TIMP-1 . Results: The obtained results showed a significant increase in serum ALT, AST, total Bilirubin and GGT and significant decrease of Albumin in liver disease groups (I, II and III) compared with Group IV. Significant increase in serum MMP9, TIMP1 in groups (I, II and III) when compared with HI group (IV). Significant correlation was recorded between MMP9 and TIMP1 in one hand and between each one with AST, T. bilirubin and Albumin concentration. Serum concentrations of TNF-α, AFP were elevated significantly in HCC patients compared to LC and CH but the difference between LC and CH was elevated significantly only ($p<0.0001$) in TNF-α. Significant association was recorded between TNF-α, LDH, AFP, ALT and AST Conclusion: MMP9 and TIMP1 could be used as new biomarker for evaluating disease progression of HCV-chronic liver disease

**Key words:** - Hepatitis C virus; Liver fibrosis; Cirrhosis; Matrix metalloproteinase-9; tissue inhibitor of Metalloproteinase Biopsy; Fibro scan.

## Introduction

Hepatitis C virus (HCV) is a major worldwide causative pathogen of chronic hepatitis, cirrhosis, and hepatocellular carcinoma[(1)]

Egypt is an endemic area of hepatitis C virus (HCV) Globally, 1 in 50 people are infected with HCV, where as approximately 1 in 7 of Egypt's 95 million people tested positive for antibodies against HCV. However, nearly 1 in 10 people carry its viral RNA and are therefore chronically infected[(2)]

Egypt has the highest prevalence of HCV infection in the world where 15% of the total population was infected and chronic hepatitis C (CHC) is a major risk factor for the development of HCC which is the second most common malignant tumor in both sexes[3]

Chronic liver disease is a major cause of inflammation and repair cause an excessive accumulation of ECM components, such as fibronectin, collagens, and proteoglycan, which are major players in the formation of scar tissue MMPs and TIMPs are the main regulators of ECM turnover in hepatic fibrosis[4]

Hepatic stellate cells, which express ECM components, MMPs and TIMPs in different timeframes are thought to play central roles in the development of hepatic fibrosis More recently, it has been suggested that hepatocytes derived MMPs are also important mediators of ECM turnover and that the MMP-cell source is likely important in determining the final fibrotic phenotype [5]

HCV infection directly modulates signaling and metabolic pathways by viral proteins. Moreover, it indirectly induces host antiviral immune responses leading to chronic inflammation. Together, these events promote liver fibro genesis[6] Hepatocellular carcinoma (HCC) ranks as the 5th most common malignant cancer and the 3rd most frequent cause of cancer leading death worldwide[7] HCC is an environmentally related cancer, with both viral and chemical carcinogens involved in multi stage process[8]However, the reasons for viral persistence and transformation from acute to chronic infection are not clear, but it is known that both viral and host characteristics can influence the outcome of the infection[9]the host response to hepatitis viruses involves various components of the immune system, including T-lymphocyte immune-regulatory cytokines[10].

TNF-α, a monocyte / macrophage-derived cytokine, is known to possess anti-neoplastic, anti-viral, and potent immunology adulatory activities [11]The majority of HCC patients are not amenable to curative therapy as they are detected at late stages [8]. Therefore, several tumor markers are used currently for the evaluation of tumor progression and prognosis of patients with HCC including AFP, Lens Culinaris agglutinin A-reactive fraction of AFP (AFP-L3) [12]. However, AFP is a fairly specific but insensitive marker for HCC. Therefore, to improve the sensitivity of HCC detection by serum markers, various markers are used in combination with AFP [13].

Lactate Dehydrogenase (LDH) is an oxides reeducates which catalyzes the inter conversion of lactate and pyruvate. When disease or injury affects tissues containing LDH.[14] the cells release LDH into the bloods team, where it is identified in higher than normal levels, has been recognized as an indirect marker of the extent of tumor hypoxia a key biological mechanism for the development of treatment resistance in cancer cells´ Therefore this study was conducted to evaluate the clinical significance of TNF-α level and its correlation with the activity of LDH and GGT in HCV-progressive liver disease.[15]

Several biochemical indicators have been discussed as potential noninvasive serum/plasma markers of fibro proliferation. Among them the matrix Metallo proteinases (MMPs) and their tissue inhibitors (TIMPs) have been shown by several groups to correlate more or less closely with the development of cirrhosis, the extent of toxic damage to the liver in alcoholic liver disease, and the inflammatory activity in patients with chronic viral hepatitis [16]. In the liver, pathological accumulation of the extracellular matrix (ECM) is the main feature of fbrogenesis; that indicates the imbalanced rate of increased matrix synthesis to decreased breakdown of connective tissue proteins which is regulated by the matrix metalloproteinase (MMPs) [17]. MMPs are a family of zinc-dependent extracellular end peptidase enzymes that play a vital role in the proteolysis of structural and signaling components of the extracellular matrix (ECM) and influence cell differentiation, migration, invasion, and proliferations of cells [18] MMPs are synthesized by hepatic stellate cells that are involved in degradation of these extracellular matrix proteins (fibrolysis). The family of MMPs consists of collagenases, gelatinases and recently described membrane type MMPs (MT-MMPs). MMPs are secreted in latent form and their activation is regulated by a family of tissue inhibitors of Metalloproteinase (TIMPs) [19] GGT has also been taken into account in the evaluation of patients with chronic HCV infection because the enzyme level is frequently increased in these cases; some authors have suggested that these changes may be related to bile duct damage, to liver disease progression, or to a poor response to therapy. Although many explanations for the GGT alteration frequently observed in patients with chronic HCV infection have been suggested, its true meaning remains unclear [20].

Therefore, the present work was planned to evaluate serum levels of MMP-9 and TIMPs as serum markers of disease progression in HCV chronic liver disease and to study its correlation with GGT activity, liver function tests and HCV viral load.

## Patients and Methods

The study included 35 patients (30men and 5 women) suffering from chronic liver disease admitted at Gastro-Entrology Surgical Center (GEC), Mansoura University from April 2016 to January 2017 and 25 Healthy individuals (15 men and 10 Women, mean age 25.3±4.63yrs) used as control group.

All patients were subjected to clinical examination, imaging radiology, laboratory investigation and histopathological diagnosis. The studied groups were categorized into: 14 patients (13 men and 1 woman; mean age 53.43±9.46yrs) with HCC associated with HCV infection, 11 patients (9 men and 2 women; mean age 52.64±9.14yrs) with LC associated with HCV infection and 10 patients (7 men and 3 women; mean age 48.9 ± 12.4 yrs) with Chronic Hepatitis.

**Biochemical and Virological Analysis**

Blood samples were collected from all groups; a part of serum samples were used immediately for measuring the activity of the biochemical parameters (Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), total bilirubin, albumin, gamma glutamyl transferase (GGT) and lactate Dehydrogenase (LDH) (Hitachi cobas C311 Analyzer) and detection of Anti-HCV by third generation (Biochem Immunosystem Company) [21].

HCV-RNA was Quantitavely detected using transcription polymerase chain reaction (RT-PCR) according to the method described by [22]. Serum AFP was detected using AFP kit (Abbott Laboratories, USA) and the results were automatically calculated using 1Mx Abbott equipment. In vitro human TNF-alpha ELISA kit (Ray Biotech, Inc., www.raybiotech.com) was used for the quantitative measurement of TNF-alpha in serum[23], the rest of serum samples were stored at -20°C until used for the evaluation of Matrix Metalloproteinase (MMP) and Tissue Inhibitor of Metalloproteinase (TIMP).

**Detection of MMP-9 and TIMP-1**

Serum concentration of MMP-9 and TIMP-1 Were measured by ELISA Technique using Kit of oncogen research products company (Sandiago, USA) according to the method of [24].

## Statistical analysis :-

Continuous variables were expressed as mean±SD and categorical variables were expressed as frequencies and percentages. To calculate the significance between categorical variables; Chi-square test or Fisher's exact test was used and the difference in continuous variables, Kruskal Wallis and Mann-Whitney U test was used. Linear regression analysis was used for correlation's statistical analysis. Differences between variables were considered significant at $p<0.05$. All calculations were performed using the (SPSS, 17.0 software)

## Results

The obtained results demonstrated in table (1) revealed that, serum levels of ALT, AST, total Bilirubin and GGT were elevated in HCC and LC compared with HI group. However, serum Albumin concentration was significantly decreased in HCC, LC and CH when compared with HI control group. Significant difference was recorded between LC and CH in ALT ($p= 0.004$) and T. Bilirubin ($p<0.02$). Highly significant difference was recorded compared to HI with HCC ($p<0.0001$ in Albumin, ALT, AST, T.Bilirubin; $p=0.005$ in GGT), with LC ($p<0.0001$ in ALT, AST, T. Bilirubin, GGT), with CH ($p=0.001$ in ALT, AST, T. Bilirubin, GGT and $p=0.039$ with Albumin). According to HCV infection, significant difference ($p= 0.039$) was recorded in GGT only between LC positive cases for HCV infection.

The obtained results demonstrated in table (2) revealed that, a significant increase in serum levels of MMP9 and TIMP-1 were recorded in liver disease groups HCC, LC and CH compared with HI group.

Within all studied group, significant difference (p< 0.0001) was recorded between HCC and LC infection in TIMP-1. Also, significant difference was detected between HCC, LC and CH in MMP9 (p=0.001) and TIMP-1(p=0.004). Significant difference between LC and CH in MMP9 (p=0.002) and TIMP-1(p=0.001). Highly significant difference was recorded compared to HI with HCC and LC (p<0.0001 in MMP9 and TIMP-1), with CH (p<0.001 in MMP9 and TIMP-1).

Table (3) showed that, there is a significant correlation between MMP9 with AST (r=0.315, p=0.014), T.Bilirubin (r=0.0.529, p<0.0001) and serum Albumin (r=-0.611, p<0.0001). Also, a significant correlation was recorded between TIMP-1 and AST (r=0.279, p=0.031), Bilirubin (r=0.480, p<0.0001), Albumin (r=-0.498, p<0.0001). GGT was associated significantly with liver enzymes ALT (r=0.761, p<0.0001) and AST (r=0.690, p<0.0001). Significant positive correlation was detected between MMP9 and TIMP-1 in all study group (r=0.906, p<0.0001) (Fig 1).

Serum concentrations of AFP, LDH, GGT and TNF-α in all individuals were listed in table (4). Significant difference was recorded between HCC and LC in AFP (p<0.0001), LDH (p=0.001), and TNF-α (p<0.0001) and the difference between HCC and CH was detected significant as regard to AFP (p=0.003), LDH (p=0.008), and TNF-α (p<0.0001). However, the difference between LC and CH patients was also highly significant (p<0.0001) in TNF-α only. Compared to HI, significant difference was recorded with HCC (p<0.0001) as regard to AFP, GGT, LDH, TNF-α; with LC as regard to LDH and TNF-α (p<0.0001) and GGT (p=0.005); with CH patients, the difference was considered significant in GGT and LDH (p<0.0001) and in TNF-α (p=0.019). However, there is no significant difference as regard to AFP neither between HI with either LC or CH nor between LC and CH.

**Table (1) Clinical characteristics and laboratory investigation of the studied groups**

| | HCC (n = 14) | LC (n = 11) | CH (n = 10) | H I** (n = 25 ) | *p value* |
|---|---|---|---|---|---|
| Alb. (gm/dl) | 2.82±0.364 | 3.19±0.689 | 3.49±1.160 | 4.49±0.263 | <0.0001 |
| T.Bili (mg/dl) | 2.65±0.818* | 4.1±3.81 | 1.68±0.979* | 0.612±0.133 | <0.0001 |
| AST ( U/ml) | 53.35±14.99 | 54.09±24.49 | 70.50±40.14 | 23.88±5.270 | <0.0001 |
| ALT (U/ml) | 36.07±7.529* | 43.63±16.82 | 69.40±41.75* | 22.640±3.95 | <0.0001 |
| GGT (U/ml) | 37.57±12.27# | 53.36±29.06# | 71.60±81.26 | 23.68±9.44 | 0.001 |

Data are presented as (Mean ± S.E). LC liver cirrhosis, CH chronic Hepatitis and HI Healthy Individual

#significant difference (p= 0.039) between HCC and LC in GGT

*Significant difference between HCC and CH in ALT (p= 0.004) and T. Bilirubin (p=0.02)

**Highly Significant difference was recorded compared to HI with HCC (p<0.0001 in Albumin, ALT, AST, Bilirubin and LDH; p=0.005 in GGT), with LC ( p<0.0001 in ALT, AST, T. Bilirubin, GGT, LDH ), with CH (p=0.001 in ALT, AST, T. Bilirubin, GGT, LDH and p=0.039 with Albumin).

**Table (2) MMP9 (ng/ml) andTIMP1 (ng/ml) in patients with HCC, LC, CH and HI**

| | HCC | LC | CH | HI** |
|---|---|---|---|---|
| MMP9 (ng/dl) | 6584.28±649.13* | 6836.36±219.19@ | 3575.0±1296.20*@ | 2884.4±294.548 |
| TIMP-1 (ng/dl) | 616.4286±93.20#* | 880.9091±129.34#@ | 439.0000±184.23*@ | 315.8000±44.22 |

Data are presented as (Mean ± SD).

#significant difference (p< 0.0001) between HCC and LC in TIMP-1

*significant difference between HCC and CH in MMP9 (p=0.001) and TIMP-1(p=0.004)

@significant difference between LC and CH in MMP9 (p=0.002) and TIMP-1(p=0.001)

**Highly Significant difference was recorded compared to HI with HCC and LC (p<0.0001 in MMP9 and TIMP-1), with CH (p<0.001 in MMP9 and TIMP-1).

**Table (3)**

**Correlation between MMP9 and TIMP-1 with liver biochemical investigations in patient of study groups**

| | ALT | AST | T.Bilirubin | Albumin | GGT | MMP9 | TIMP-1 |
|---|---|---|---|---|---|---|---|
| MMP9 | 0.078<br>0.552 | 0.315*<br>0.014 | 0.529**<br><0.0001 | -0.611**<br><0.0001 | 0.101<br>0.445 | 1 | 0.906**<br><0.0001 |
| TIMP-1 | 0.101<br>0.442 | 0.279*<br>0.031 | 0.480**<br><0.0001 | -0.498**<br><0.0001 | 0.181<br>0.166 | 0.906**<br><0.0001 | 1 |
| GGT | 0.761**<br><0.0001 | 0.690**<br><0.0001 | 0.268*<br>0.039 | -0.317*<br>0.014 | 1 | 0.101<br>0.445 | 0.181<br>0.166 |

** Correlation is significant at the p<0.001 level

* Correlation is significant at the p=0.05 level

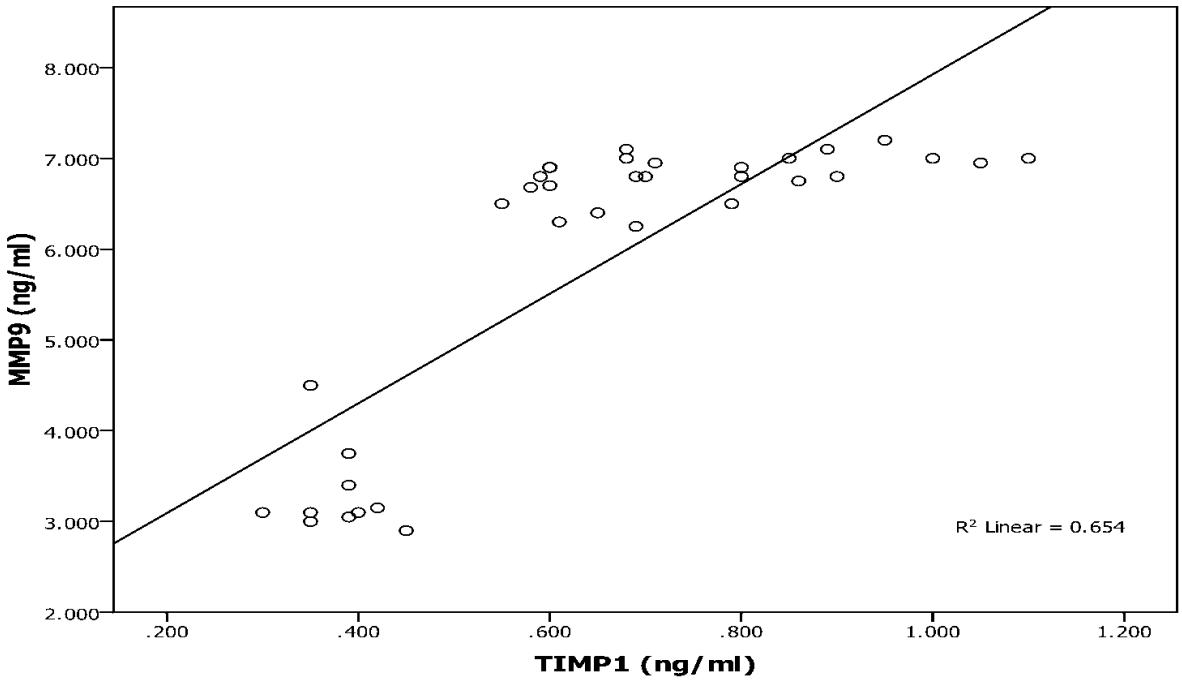


**Figure (1): correlation between MMP9 and TIMP-1 in patients with chronic liver disease.**

**Table (4) Serum level of AFP, LDH, GGT, TNF-α in patient with HCC, LC, CH and HI**

| | HCC N=14 | LC N=11 | CH N=10 | HI N=25 |
|---|---|---|---|---|
| **AFP (ng/ml)** | | | | |
| **mean±SD** | 170.98±284.0•* | 6.15±3.39• | 24.9±61.6* | 5.03±1.8 |
| **% of positivity** | 11/14(78.6%) | 0/11(0%) | 1/10(10%) | 0/25(0%) |
| **LDH (u/l)** | | | | |
| **mean±SD** | 413.2±84.6•* | 320.0±41.51• | 341.6±114.95* | 217.3±51.1 |
| **% of positivity** | 14/14(100%) | 12/14(85.7%) | 7/10(70%) | 6/25(24%) |
| **GGT (u/l)** | | | | |
| **mean±SD** | 76.3±75.5 | 37.6±12.3 | 71.6±81.3 | 23.7±9.5 |
| **% of positivity** | 8/14(57.5%) | 0/11(0%) | 3/10(30%) | 1/25(4%) |
| **TNF-α (pg/ml)** | | | | |
| **mean±SD** | 520.6±48.4•* | 414.3±43.1•+ | 315.5±34.8*+ | 288.8±25.5 |
| **% of positivity** | 14/14(100%) | 13/14(92.9%) | 2/10(20%) | 1/25(4%) |

•The difference was considered significant between HCC and LC as regard to AFP ($p<0.0001$), LDH ($p=0.001$), TNF-α ($p<0.0001$)

*The difference was considered significant between HCC and CH as regard to AFP ($p=0.003$), LDH ($p=0.008$), TNF-α ($p<0.0001$)

+The difference was considered significant between LC and CH as regard to TNF-α ($p<0.0001$)

## Discussion

Hepatitis C virus (HCV) infection, in addition to being a major cause of chronic liver disease, is a major cause of liver cancer; HCV can be considered a human tumor virus. The HCC incidence has increased sharply in recent decades, which can be partially attributed to the increase in chronic HCV infection [(25)]

The biochemical evaluation of chronic HCV carriers is initially carried out by analyzing serum aminotransferase that are often high in these patients. The wide utilization of such enzymes is due to the fact that the aminotransferase are considered to be indicators of Hepatocellular damage, thus reflecting active disease in accordance with other previous studies a significant increase was detected in serum ALT, AST, total bilirubin and GGT activities in liver disease groups compared with HI group. The elevated levels of serum enzymes are indicative of cellular leakage and loss of functional integrity of the cell membrane in liver which could be taken as an index of liver damage, liver cell destruction results in the leaking out of tissue contents into the blood stream [(26)]

The obtained results in our study showed a significant reduction of serum albumin levels in HCC, LC and CH patients compared with HI group; these results came in accordance with [(27)] The decreases in albumin contents in liver might be due to increased catabolism of

proteins and defect in protein biosynthesis that might be due to the consequences of disruption and dissociation of polyribosomes from rough endoplasmic reticulum and the decrease in the amount of total protein may be also attributed to the decrease in the amount of albumin [28].

TNF-α plays a central role in the host's immunomodulatory response to infective agents and hepatitis infection is associated with increased transcriptional expression of the TNF-α gene in the liver with high serum levels of TNF-α [29], the level of TNF-α was elevated significantly ($p<0.0001$) in the sera of HCC patients compared to LC and CH and also, elevated in LC than CH ($p<0.0001$). Elevated serum TNF-α level have been observed by other researchers even in patients with mild liver inflammation, indicating that this cytokine could be used as a predictor of liver inflammation [30]. TNF-α level was not correlated with ALT, AST, or viral load in current study and these results are in consistence with other reports, that, serum TNF-α level was not correlated with serum ALT or AST activities neither in HBV nor in HCV infected patients [31]. Such results have also been reported by other authors and it is concluded that, measurement of TNF-α levels reflects liver injury despite normal levels of liver enzymes [32].

LDH is a commonly used serum biomarker, which is easily and cheap to detect and, thus, appropriate for the use in routine clinical practice [15]. In current study, serum concentration of LDH was highly elevated in patients with HCC than in LC ($p=0.001$) and CH ($p=0.008$) but there is no significant difference between LC and CH. Therefore, elevated LDH is a possible indicator of disease progression [33]

In current study, the level of GGT was significantly increased in LC and CH compared with healthy control group. Some authors have suggested that the GGT alteration found in chronic hepatitis and in liver cirrhosis should be related to increased GGT synthesis in the liver as an adaptive response to the pathological changes that take place in such diseases. As a result, there is an over flow of the enzyme into the blood stream [34].

However, serum GGT activity is a microsomal enzyme of the biliary canalicular membrane that is markedly raised in acute parenchyma damage from any cause. It is used to confirm that the rise in ALT and AST is hepatic in origin. Therefore, serum AST, ALT and γ-GT are the most sensitive markers employed in the diagnosis of liver diseases [35]. In current study, significant positive correlation was recorded between GGT with ALT and AST. These results agree with previous studies [36] who demonstrated a highly significant correlation between serum levels of GGT and AST and also agree with [37] who demonstrated a highly significant correlation between serum levels of GGT and ALT but disagree with [38] who found no such association between GGT and ALT.

MMP9 and TIMP1 level are significantly higher in both HCC and cirrhotic cases than in healthy control subjects. The degradation of the extracellular matrix by tumor cells was a critical step in tumor metastasis, as the basement membrane and interstitial stroma represent the first barrier to tumor spread although several proteolytic enzymes are involved in this process. MMP-9 plays a critical role, since it degrades Type IV collagen and contributes to loss of integrity of the basement membrane around blood vessels and under mesothelium layer [39].

In current study, highly significant difference was recorded between MMP9 and TIMP-1 in chronic liver disease when compared with Healthy control group, Also MMP9 mean serum levels were significantly higher in chronic HCV patients than in controls ($p<0.05$) as reported by [40] but others reported that serum MMP9 was significantly lower in patients with chronic HCV than in controls [41]. Therefore, a number of enzymes are involved in the degradation and the synthesis of ECMs in the liver; and progression of hepatic fibrosis to Cirrhosis and HCC may be associated with the imbalance between the activities of MMPs and TIMPs.

Serum levels of TIMPs, as fibrogenic factors and MMPs, as fibrolytic factors in chronic liver diseases caused by viral infections showed that TIMP-1 level was significantly higher in HCC, LC and CH patients than in normal control in accordance with [42] who detected significant elevation with both MMP9 and TIMP-1. In current study, significant correlation was recorded between serum MMP9 level and TIMP-1 on one hand and between each one of them with serum albumin, serum bilirubin, and albumin concentration among all the studied groups.

In current study MMP9 and TIMP-1 were significantly higher in liver cirrhotic group compared to chronic hepatitis patients. These results are in agreement with [43] who reported that MMP9 and TIMP1 appears to play a key role in the inflammatory processes occurring in the liver of chronic HCV patients and independent association has been noted between hepatic inflammatory activity. These results suggesting that, serum MMP9 and TIMP-1 levels consider mirrors liver tissue expression, and serum MMP9, TIMP1 could be used as new biomarker for liver disease progress, without performing invasive procedures for diagnosis.

***In conclusion***, this study shows that the activity of MMP-9 and TIMP-1 might be markers of Chronic liver diseases Chronic Hepatitis HCV, Liver cirrhosis and HCC). Elevated levels of MMP9 and TIMP-1 in the Chronic liver diseases patients indicated that CH, cirrhosis and HCC had developed. Additionally, MMP9 and TIMP-1 could be used as serum markers for evaluating disease progression in HCV chronic liver disease.

## Recommendations:

MMP9 and TIMP-1 can be used as biomarkers for diagnostic of chronic liver disease to determine the degree of injury in liver tissue and determined the liver cirrhoses, fibrosis and HCC with Individuals

with focal lesions in ultrasound examination require further examination with triphasic computed tomography (CT), magnetic resonance imaging (MRI), confirm a diagnosis of (HCC) without need of liver biopsy.

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**List of Abbreviations:**

(AFP) Alpha Feto Protein; (ALT) Alanin amino transferaes; (AST) Aspartate amino transferaes; (CT) computed tomography; (CH) Chronic Hepatitis; (ECM) Extra Cellular Matrix; (ELISA) Enzyme-linked immunosorbent assay (GGT) Gama Glutamyl Transferase; (HCC) hepatocellular carcinoma; (HCV) Hepatitis C virus; (LC) Liver Cirrhosis; (LDH) Lactate Dehydrogenase; (MMP)matrix metalloproteinase; (TIMP) tissue inhibitor of metalloproteinase; (PCR) Polymerase Chain Reaction; (TNF-α) Tumor Necrosis Factor-α.

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**الملخص**: تهدف هذه الدراسة إلى تقييم الدلالة الإكلينيكية لإنزيم الميتالوبروتيناز- 9 كمنبئ تشخيصي في حالات التهاب الكبد الفيروسي-س المزمن وإمراض الكبد من تليف او تشمع اوسرطان الكبد وكذلك تهدف هذه الدراسة إلى تحديد مدى وجود علاقة بين مستوى إنزيم الميتالوبروتيناز-9 فى الدم ومدى تأثروظائف خلايا الكبد خاصة انزيمات الكبد و نسبة الصفراء والألبومين وجاما جلوتاميل ترانسفيريز وكذلك مع درجة شدة المرض وكذالك مقارنة بين مقدار التغير فى مستوى الميتالو بروتينيز -9 فى حالات سرطان الكبد مع التغير فى مستوى دلالات الاورام الفا فيتو بروتين.

وقد أجريت هذه الدراسة على خمسة وثلاثون مريضاً تم اختيارهم جميعا من مركز جراحه الجهاز الهضمى – جامعة المنصوره بالإضافة إلى خمسة وعشرون من الأصحاء الهدف منهم مقارنتهم بمجموعة المرضى محل الدراسة.

***الخلاصة:*** أظهرت الدراسة التي أجريت على المجموعات المرضيه المختلفه عن وجود زيادة في تركيز الانين امينو ترانسفيراز ، أسبارتيت امينو ترانسفيراز، الفوسفاتيز القلوى ، الصفراء الكلية، الهابتوجلوبين (لاكتيت دى هيدروجينيز، جاما جلوتاميل ترانسفيريز و إلفا فيتو بروتين , TNF-α كما وجد نقص فى تركيز الألبومين مقارنة بالمجموعه الضابطه.

وأوضحت الدراسة أن مستوى إنزيم الميتالو بروتينيز -9 والمانع النسيجي للميتالو بروتينيز-1 يتناسب طرديا مع مقدار التغير فى التركيب الخلوى للخليه الكبديه ومدى حدوث تغيرات باثولوجيه على الانسجه.



**الكلمات المفتاحية:** فيروس الالتهاب الكبدي؛ تليف الكبد. التليف الكبدي؛ ماتريكس ميتالوبروتيناز-9؛ مثبط الأنسجة من خزعة ميتالوبروتيناس. مسح فبرو.