Medical Science Journal for Advance Research

Vol. 6, No.1, March 2025
e-ISSN: 2774-4892

Assessment of IL-18 in HCV with T2DM in Al-Najaf Province

Zeena Kareem Gihad
Department of Community Health Techniques, College of Health and Medical Techniques, Kufa, Al-Furat Al-Awast Technical University, Iraq.
E-Mail: Zina.jehad@atu.edu.iq

ABSTRACT

Background: *The study's objective is to look at the Hepatitis C virus in Al-Najaf province patients who have diabetes mellitus. In order to accomplish this, a total of 85 patients (44 men and 41 women) from AL-Hakeem Hospital in AL-Najaf province who were suspected of having diabetes and the hepatitis C virus , during the period from April 10, 2024, to January 5, 2025. Their age are ranged between (≥20 and ≤41). The detection of IgG specific for HCV was done by the use of third generation of ELISA technique, and the Estimation of human IL-18 in serum was performed using sandwich-ELISA. The study's findings showed a significant prevalence of disease in adults, with 38% of those aged ≤41 and 26% of those aged 31–40 years having the condition. The findings showed that groups of patients with diabetes had higher levels of specific anti-HCV IgG antibodies than groups without diabetes .The percentage of HCV patients without diabetes was 82.1%, whereas the percentage of HCV patients with diabetes was 17.9%. Patients with diabetes exhibited significantly greater blood levels of IL-18 (50.3 pg/ml) than those without diabetes (control group), with a mean concentration of 5.88 pg/ml, P<0.05, according to the current study. The study found a substantial difference in serum levels of IL-18 between HCV patients with diabetes and those without the disease. With a mean value of 44.97 pg/ml (P<0.05), it is clear that HCV patients with diabetes had higher blood levels of IL-18 (55.39 pg/ml) than HCV patients without diabetes.*

Keywords: HCV virus , IL-18 and T2DM.

Article Information
Received: January 7, 2025; Revised: February 21, 2025; Online: March, 2025

INTRODUCTION

The viral condition known as hepatitis C is brought on by a hepatotropic virus that targets liver cells and causes liver scarring, which usually becomes noticeable after many years (HCV) (1). A participant of the Flaviviridae family, HCV is a genus of Hepaciviruses that are extremely tiny, measuring between 55 and 65 nm, having a single positive sense, ribonucleic acid (RNA) genom, and encapsulated (2). In addition, three to elevent percentages of patients will progress liver cirrhosis in 20 years, which is associated with the risk of hepatocyte disappointment and liver cancer. About 170 million people worldwide are infected with HCV; 20–30% of patients recover on their own, but 70–80% of patients remain chronically infected (3). Bryoglobulinemia, thrombocytopenia, Sjogren's syndrome, porphyria cutanea tarda, lichen planus, B-cell lymphoproliferative, insulin resistance (IR), and type 2 diabetes mellitus (T2DM) are the most prevalent extrahepatic symptoms (EHM)
(4).

Numerous trainings have observed the connection among HCV infection and the

https://doi.org/10.46966/msjar.v6i1.247

Published by: READ INSTITUTE

progress of diabetes, and it has been found that patients with HCV infection have a greater occurrence of type two diabetes than patients with other types of chronic hepatitis. HCV and T2DM are chronic diseases that significantly increase morbidity and mortality(5). Any stage of a hepatitis infection can result in the development of diabetes and IR. A number of hypotheses have been proposed to explain how HCV causes IR and hyperglycemia in CHC patients. It mostly causes IR by interfering with the liver cells' insulin signaling system and inflammatory cytokines including interleukin-18 regulation (IL-18)(6).

Direct percutaneous blood exposure—injection drug use, transfusion, or transplantation from infectious donors—is the primary method of acquiring an HCV infection, even though mucosal contact with blood or serum, such as during cosmetic procedures, sexual partner infections, and perinatal transmission, is less effective (7). The virus's capability to prevaricate the host's immune system and resist antiviral therapy is connected to its capability to infect the host for the rest of their life. Typically, HCV exposure leads to a chronic infection that is accompanied by a persistent infection (8).

Cytokines are essential for liver formation and renewal as well as inflammatory progressions such liver fibrosis ,viral liver disease, and liver cirrhosis. They mediate both physiologic and pathologic processes in the liver (9). Interleukin-18, a pro-inflammatory cytokine that belongs to the IL-1 superfamily and aids in promoting Th1's pro-inflammatory response, is produced by macrophages and other cells (10). It can control both adaptive and innate immune responses by influencing B cells, T cells, dendritic cells, monocytes, and natural killer (NK) cells (11). It has several functions in chronic inflammation as well. (12). IFN-γ is created by natural killer (NK) cells in response to IL-18, which promotes Th1 cell proliferation and increases the cytotoxic influence of NK cells (13). Interleukin-18, or IL-18.

Cytokines have been linked to the directive of both acquired and innate immunological reactions and are important in autoimmune infections by controlling the "Th1- and Th2-immune responses"(14). Non-hematopoietic cells and hematopoietic cells can both produce IL-18. Kupffer cells, which are liver-resident macrophages, were initially shown to synthesize it even when they were not activated and were at rest (15). The training aimed to determine the occurrence of type two diabetes mellitus in people with chronic HCV infection by analyzing IgG antibodies to HCV infection using third-generation ELISA, and measuring the blood levels of IL-18 in individuals with HCV infection and HCV-T2DM.

METHOD

Get 85 blood samples from hepatitis C virus patients. In order to extract serum for serological testing, five milliliters of venous blood were collected in coagulate gel tubes and centrifuged. The serum were placed in sterile appendrofe tubes in three times and stored frozen at -20 C˚for the ELISA test to determine the level of IL-18 and HCV. The blood was centrifuged at (3000rpm) for two minutes later being left at room temperature for about half an hour to allow for coagulation.

1-Detection of hepatitis C virus

The third-generation ELISA method was employed to identify HCV-specific IgG. The third generation HCV ELISA kit detects HCV antibodies using a two-step incubation process using a solid phase, indirect ELISA test. Recombinant, highly immunoreactive antigens that match the core and non-structural sections of HCV are pre-coated onto polystyrene micro well strips (third generation HCV ELISA). The test was carried out following the guidelines provided by the manufacturer.

2-Estimation of human IL-18 in serum

The ELISA kit use the sandwich-ELISA technique. This kit comes with a 96 micro titer plate that has been adsorbed with an IL-18-specific antibody. "Once the samples and standards were placed in the appropriate wells, the specific antibody was combined with them. The well was then filled with a biotinylated detection antibody specific to IL-18 and allowed to bind. The wells were filled with the Avidin-Horseradish Peroxidase (HRP) conjugate and then incubated. Following the removal of the unbound components from the wells, chromatogenic substrates were added to each well and allowed to incubate". Only when IL-18, biotinylated detection antibody, and Avidin-HRP conjugate are present will the wells' color change. A stop solution is added to each well to halt the enzyme-substrate reaction and change the color from blue.

Ethical Committee

Technical University of Al-Furat Al-Awast oversaw and suggested this effort. Without the use of extra materials or alterations, and with permission from the Iraqi Ministry of Health's Medical Ethics Committee, all of the samples utilized in this study were acquired in compliance with the research protocols for each kind.

Statistical Analysis

A computerized database structure was created from the data. Microsoft Excel 2010 in conjunction with the computer program Graph Pad Prism (version 6) was used to perform the statistical analyses.

Results were presented with $p < 0.05$ being observed as statistically significant. The correlation coefficients were used to find relationships between IgG and IL-18.

RESULT

Between 10 April 2024 A.D. and 5 January 2025 A.D., a total of 85 individuals (44 male and 41 female) from"AL-Hakeem Hospital in AL-Najaf province"were suspected of having diabetes and the hepatitis C virus. They are between the ages of 20 and 41. The patient groups were distributed into the following categories:

1-Distribution of patients depending on the age

The study's findings showed a significant prevalence of illness in adults, with 38% of the (≤41) age group and 26% of the (31–40) age group having the condition, respectively (table 1).

Table-1:Show the distributions of patients according to age:

Age Group	Total N.(%)
(≥20)Years	20(24%)
(21-30_Years	11(13%)
(31-40)Years	22(26%)
(≤41) Years	32(38%)
Total	85(100%)

2-Distribution of hepatitis C patients according to gender

The hepatitis C patients were split into two groups (M and F) based on their gender. The current study revealed that the male group had the largest proportion, including 44/85 (52%) patients, while the female group had 41/85 (48%) patients, as seen in figure (1).

3-Distribution of hepatitis C patients according to T2DM

The findings showed that groups of patients with diabetes had higher levels of specific anti-HCV IgG antibodies than those without diabetes. Based on their type 2 diabetes, the hepatitis C patients were split into two groups (A and B).According to figure (2), group A represents HCV patients without diabetes, which made up 82.1% of the total, and group B represents HCV patients with diabetes, which made up 17.9% of the total.

4-Distribution of hepatitis C patients according to concentration of IL-18

According to the current investigation, patients with diabetes had a substantially higher blood level of IL-18 (50.3 pg/ml) than patients without diabetes (control group), which had a mean concentration of 5.88 pg/ml $P < 0.05$, figure (3).

5- Comparison IL-18 Level between HCV Patients with diabetes and without diabetes

According to the results of the current investigation, HCV patients with diabetes and those without diabetes had significantly different blood levels of IL-18. It is evident that HCV patients with diabetes had higher blood levels of IL-18 (55.39 pg/ml) than HCV patients without diabetes, with the mean. concentration being 44.97 pg/ml, $P<0.05$, figure (4).

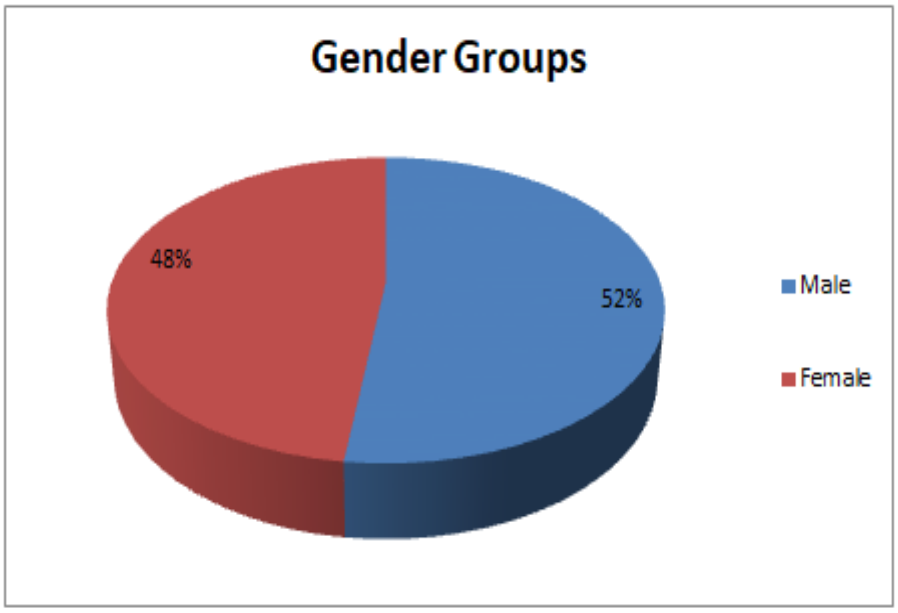

Figure-1 : Distribution of HCV infected patients according to gender

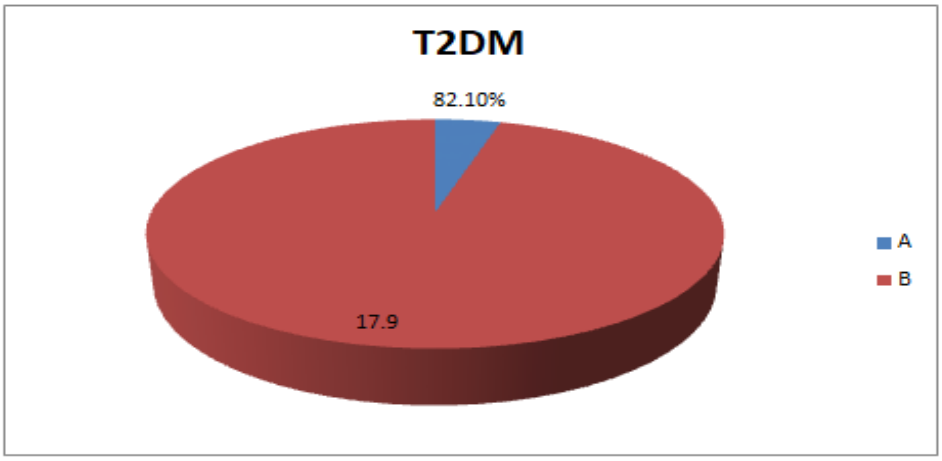

Figure 2 : Distribution of HCV infected patients according to T2DM

A:the patients without diabetes.
B: the patients with diabetes.

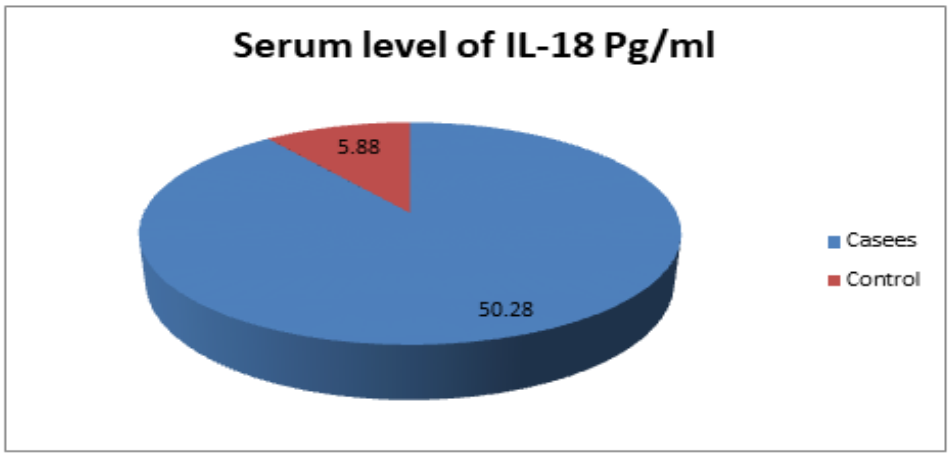

Figure-3:Distribution of HCV patients according to concentration of IL-18.

Cases: the patients with diabetes.
Control:the patients without diabetes.

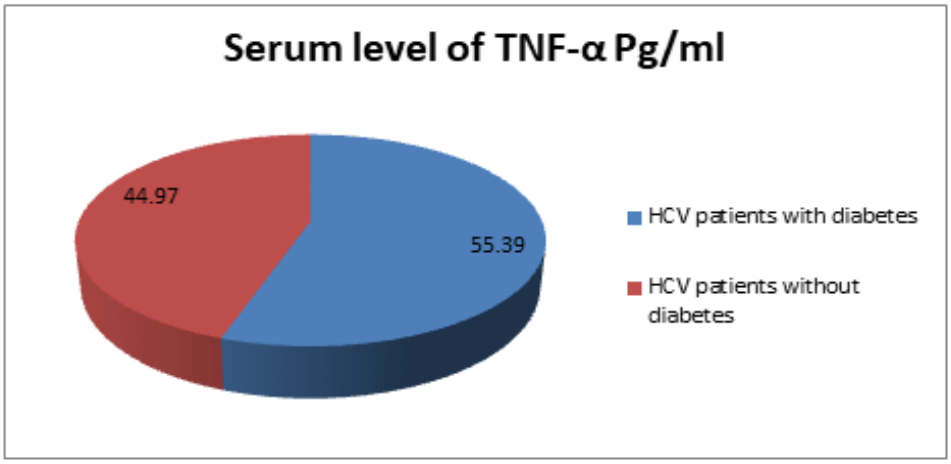

Figure-4:Comparison IL-18 Level between HCV Patients with diabetes and without diabetes

DISSCUSION

The hepatitis C virus's significance as a danger influence for developing type 2 diabetes was identified in the current study using single markers. The laboratory approach relies on the immunological metric IL-18 and the detection of particular anti-HCV IgG by ELISA.

Hepatitis C virus infection and type two diabetes mellitus are prevalent diseases that have a major global impact. Patients who have gotten hepatitis C frequently develop type two diabetes mellitus, and a substantial amount of research and data supports the idea that "that HCV infection is a risk factor for developing T2DM" (16).

One of the most effective diagnostic techniques for identifying anti-HCV antibodies generated in reaction to viral infection is ELISA. Since the third generation of ELISA for HCV can identify antibodies to four recombinant viral proteins (NS5, NS4, NS3, and core protein), it is more sensitive and specific than its predecessors (17).

According to Wang *et al.* (2003), people between the ages of 50 and 65 have a higher frequency of anti-HCV IgG than do younger people. Additionally, they stated that women are more likely than men to be suspected of having HCV (18).

In Pakistan,"Amjad *et al.* (2010) found that the occurrence of HCV rose as the number of individuals grew, with the maximum prevalence occurring in those over 41. However, the findings showed that males reported a higher frequency of HCV infection than females (19).

Because the core-encoding region of HCV is sufficient to induce IR by the previously defined mechanism either directly or indirectly, the pathophysiology of HCV-associated type 2 diabetes mellitus consists of insulin resistance, increased hepatic tumor necrosis factor alpha, elevated hepatic glucose production, and a defect in insulin secretion. T2DM in individuals with HCV was found to be mostly caused by these two variables (20). Second, a large percentage of pre-existing risk factors for diabetes, including advanced age and a positive family history, also significantly contribute to the likelihood of developing diabetes in people with HCV(21).

According to Southeast Asian reports, among HCV-positive individuals under 40 years of age, the occurrence of type two diabetes was 31.5% (114/361). Additionally, new research indicates that the prevalence of type two diabetes is three times greater in patients with HCV seropositive status than in the control group that is not infected with HCV (22).

According to the findings of two earlier investigations, type 1 diabetic individuals have higher circulating IL-18 concentrations than nondiabetic people (23). Nicoletti *et al.*'investigation revealed that newly diagnosed type 1 diabetes individuals' IL-18 concentrations remained unchanged. There have also been reports of elevated circulating IL-18 levels in type 2 diabetes, with insulin resistance serving as the primary underlying cause (24).

Further studies have shown that raised ranks of mingling plasma IL-18 are strongly correlated by the severity of HCV infection. IL-18 and hepatic histological activity were positively correlated in 20 patients with chronic hepatitis C (25).

CONCLUSION

According to the study's findings, those over 41 who have an HCV infection are more likely than those in other age groups to develop type 2 diabetes. It was also determined that patients with HCV are at a greater danger of evolving type II diabetes. Lastly, a high level of the inflammatory cytokine IL-18 is essential for HCV pathogensis, which results in type 2 diabetes.

REFERENCES

1- **Ryan, K. and Ray, C. (2004).** Sherris Medical Microbiology (4th ed.). McGraw Hill. pp. 551–2.

2- **Kolawole, O. Aturu, E. Alabi, O. and Kassim, O. (2013).** Risk determinants to hepatitis C virus and malaria co-infection in patients attending federal medical centre Lokoja, Nigeria. World Applied Sciences Journal, 25 (2): 294-305.

3- **Rajesh N. and Sadiq K. (2012).**Seroprevalence and Risk Factors for Hepatitis C Virus Infection among General Population in Central Region of Yemen. Volume (2012), Article ID 689726, 4 pages.

4- **Huaibin, M. Juan, C. Hongfa, Z. Steven, H. Harleen, K. Stephen, C. and Swan, N. (2012).** Morphologic features of extra hepatic manifestations of hepatitis C virus infection. Clinical and Developmental Immunology, Volume 2012, Article ID 740138, 9 pages.

5- **White, D. Ratziu, V. and El-Serag, H. (2008).** Hepatitis C infection and risk of diabetes: a systematic review and meta-analysis. Journal of Hepatology, 49 (5): 831-844.

6- **Muhammad, S. Zain, I. Farukh, N. Madiha, Z. Suresh, K. and Asif, A. (2013).** Prevalence of type 2 diabetes mellitus in hepatitis C virus infected population: a Southeast Asian study. Journal of Diabetes Research, Volume 2013 (2013), 7 pages.

7- **Miriam, J. (2007).** Epidemiology of hepatitis C virus infection. World J. Gastroenterol., 13 (17): 2436-2441.

8- **Falasca, K. Ucciferri, C. Dalessandro, M. Zingariello, P. Mancino, P. and Petrarca, C. (2006).** Cytokine patterns correlate with liver damage in patients with chronic hepatitis B and C. Ann. Clin. Lab. Sci., 36:144-150.

9- **Larrubia, J. Benito-Martínez, S. Miquel-Plaza, J. Sanz-de-Villalobos, E. Gonzalez-Mateos, F. and Parra, T. (2009).** Cytokines –their pathogenic and therapeutic role in chronic viralhepatitis. Rev. Esp. Enferm. Dig., 101:343-351.

10- **Kim, S.K. Park, H.J. Chung, J.H. et al.(2014).** Association between interleukin 18 polymorphisms and alopecia areata in Koreans. J Interferon Cytokine Res. 34:349-353.

11- **Srivastava, S. Salim, N. Robertson, M. J. (2010).** Interleukin-18: biology and role in the immunotherapy of cancer. Curr. Med. Chem. 17. 3353–3357.

12- **Ide, A. Kawasaki, E. Abiru, N. et al.(2003).** Association of interleukin18 gene promoter polymorphisms in type 1 diabetes and autoimmune thyroid disease. Ann N Y Acad Sci. 1005:436–439.

13- **Zhou, J. Shang, J. Song, J. Ping, F.(2013).** Interleukin-18 augments growth ability of primary human melanocytes by PTEN inactivation through the AKT/NF-Kb pathway. Int J Biochem Cell Biol. 45:308-331.

14- **Salimi, E. Karimi-Zarchi, M. Dastgheib, S.A. Abbasi, H. Tabatabaiee, R.S. Hadadan, A. (2019).** Association of promoter region polymorphisms of IL-6 and IL-18 genes with risk of recurrent pregnancy loss: a systematic review and meta-analysis. Fetal Pediatr Pathol Taylor and Francis Ltd. 39:346–59.

15- **Liu, Z. Wang, H. Xiao, W. Wang, C. Liu, G. and Hong, T. (2010).** "Thyrocyte interleukin-18 expression is up-regulated by interferon-γ and may contribute to thyroid destruction in Hashimoto's thyroiditis". International Journal of Experimental Pathology. 91 (5): 420–5.

16- **Donna, L.; White, V.; Hashem, B. and Serag, E. (2008).** Hepatitis C infection and risk of diabetes: a systematic review

and meta-analysis. J. Hepatol., 49 (5): 831-844.

17- **Colin, C.; Lanoir, D.; Touzet, S.; Meyaud, L.; Bailly, F. and Trepo, C. (2001).** Sensitivity and specificity of third-generation hepatitis C virus antibody detection assays: an analysis of the literature. J. Viral. Hepat., 8: 87-95.

18- **Wang ,C.; Wang, S.; Yao,W.; Chang, T. and Chou, P.(2003).** Community-based Study of Hepatitis C Virus Infection and Type 2 Diabetes: An Association Affected by Age and Hepatitis Severity Status. American Journal of Epidemiology, Vol. 158, No. 12;158:1154–1160.

19- **Amjad, A.; Habib, A.; Ijaz, A.; Sheema, K.; Gulshan, Z. and Muhammad, I.(2010).** Prevalence of active hepatitis c virus infection in district mansehra Pakistan. Virology Journal, 7:334;1-5.

20- **Po-Shiuan, H. and Yen-Ju ,H.(2011).** Impact of liver diseases on thedevelopment of type 2 diabetes mellitus. World Journal ofGastroenterology, ,vol.17,no.48,pp.5240–5245.

21- **Stepanova, M. ; Lam, B.; Younossi, Y.; Srishord, M. and Younossi,Z.(2012).** Association of hepatitis C with insulin resistance and type 2 diabetes in US general population: the impact of the epidemic of obesity.Journal of Viral Hepatitis,vol.19,no.5,pp.341–345.

22- **Ali,S.; Abera, S.; Mihret, A. and Abebe,T. (2012).** Association of hepatitis C virus infection with type II diabetes in Ethiopia : a hospital-based case-control study. Interdisciplinary Perspectives on Infectious Diseases. Pp. 1-7.

23- **Eliana, M. and José, E. (2003).** Differential effect of IL-18 on endothelial cell apoptosis mediated by TNF-α and Fas (CD95). Vol. 22, Issue 5, 7, P. 142-148

24- **Yuji, M. Tetsuya Y.and Yuhei, S. (2003).** Elevated levels of interleukin-18 and tumor necrosis factor-α in serum of patients with type 2 diabetes mellitus: Relationship with diabetic nephropathy.Vol.52, Issue 5, 2003, P. 605-608.

25- **Arpita, Sh. Anuradha, C. and Ashim D. (2009).** Elevation of interleukin-18 in chronic hepatitis C: implications for hepatitis C virus pathogenesis. Immunol;128(1 Pt 2):e514–e522.

