How to Cite:
Hamoud, R. T., & Mohsen, R. T. (2022). Correlation of liver function tests and serum level interleukin-18 in patients with hepatitis B and C virus infection. *International Journal of Health Sciences*, *6*(S6), 11543–11551. https://doi.org/10.53730/ijhs.v6nS6.13208

Correlation of liver function tests and serum level interleukin-18 in patients with hepatitis B and C virus infection

Rowaida T. Hamoud
Department of Biology,College of Science, University of Al-Anbar, Iraq
*Corresponding author email: row20s1004@uoanbar.edu.com

Rana T. Mohsen
Department of Biotechnology, College of Science, University of Anbar, Al-Anbar, Iraq
Email: rana2011@uoanbar.edu.iq

Abstract---Hepatitis B virus and hepatitis C virus are among the most common Infectious agents are most commonly transmitted through the blood Still a major global health problem, this possibility A study was conducted in Fallujah General Hospital, and the Public Health Laboratory in Anbar Governorate – Iraq. Study it was conducted on 60 individuals out of (30) cases of hepatitis B and C patients and (30) healthy cases (control) who were selected according to health criteria .The following data was recorded:Age, gender, date, resident, type of injury, data were collected by Statistical units Data were analyzed using SPSS for windows (version Distributing (HBV,HCV) patients into age group revealed that < 40 year age group had the highest frequency ` (56.67)%. while the age group > 50 year recorded the lowest frequency 3 (10.00)%. Among control, the age group > 50 years had the highest frequency 14(48.28)%, followed by the age group < 40 and year 10(34.48)%. And the lowest frequency in age group 40-50 recorded 5(17.24n Most of HBV,HCV patients were males (21(70%), while female patients accounted for 9(30%). Almost approximated frequencies were reported in control (17(58.62)and 12(41.38%, respectively). Serum mean of TSB showed significant difference between (HBV,HCV) patients and control (1.145 v.s0.65 µmol/L; p<0.001),and stand. Error 0.5779, Serum mean of ALP showed a significant decrease in HBV,HCV patients compared to control (28.0667,92.4138 U/L; p>0.000,st error4.85050), The serum mean of AST was significantly increased in HBV,HCV patients compared to control (114.5 *vs*. 18.43 U/L; p < 0.00) and stand. Error 15.07,. Serum median of ALT showed a significant increase in HBV,HCV patients compared to control (53.53 *vs*. 10.26 U/L; p = 0.001) and

stand. Error 10.44, . The analysis demonstrated no significant correlations between serum level of IL-18 and LFTs, TSB (r = 0.225), ALP (r = 0.0845), ALT (r = - 0.185) and AST (r = - 0.011) an increase in the level of the concentration of interleukin-18 (IL-18) was observed in the sera of the infected patients in relation to the absorbance of each of the infected samples.

Keywords---correlation, liver function, interleukin-18, hepatitis, virus infection.

Introduction

Chronic hepatitis B virus (HBV) infection represents a complication of a major concern in public health. In 2015, the World Health Organization (WHO) estimated that 257 million people were living with chronic HBV infection. The infection resulted in an estimated 887,000 deaths, mostly due to liver cirrhosis and hepatocellular carcinoma. Clearance or persistence of HBV infection is mostly determined by host immune responses(1). Accordingly, the endemicity of HBV in Iraq was considered to be at low / intermediate level. Clearance or persistence of HBV infection is mostly determined by host immune responses. A complex interaction between HBV and an inadequate immune response is required to establish the chronicity of HBV infection . Upon infection, effective antiviral immune responses mediated by CD8+ and CD4+ T cells, as well as natural killer (NK) cells and monocytes, can result in partial or complete eradication of HBV. It has been demonstrated that acute HBV infection induces CD4+ and CD8+ T responses together with elevated production of interferon-gamma (IFN-γ). IFN-γ is prominent cytokine in clearing the virus and controlling HBV infection(2). In Iraq, a community-based study reported a prevalence of 1.6% for hepatitis B surface antigen (HBsAg). Further, the anti-hepatitis B core antigen (HBc) and anti-HBs antibodies were reported at prevalence of 9.7 and 17%, respectively(3).

A viral infection causes liver inflammation, which leads to viral hepatitis. The viral aetiologies of hepatitis have only recently been discovered, despite the fact that "epidemic jaundice" has existed since ancient civilisation. (4)Hepatitis is the most prevalent form of the infectious form of the viral disease, though it can also be non-infectious in origin. Only viruses B and C can occur acutely or chronically and cause chronic hepatitis, out of the five types of viruses that cause viral hepatitis(HAV,HBV,HCV, HDV, and HEV) (5). the most important cause of post-transfusion hepatitis is Infection with the hepatitis HBV and HCV. Furthermore, hepatitis B and C are the most common causes of chronic hepatitis in the world, and they are primarily transmitted through direct contact with blood, the use of injection drug, blood transfusions and/or blood products, and sexual relationships. Sexual relations, on the other hand, do not seem to to be the most common mode of HCV transmission. Around 350-400 million people worldwide are chronic HBV carriers, accounting for approximately 7% of the total population, whereas HCV infection affects approximately 3% of the global population, or 160 million people(6).Hepatic viruses alter cellular pathways that influence liver homeostasis and disease development during chronic infection by

continuously modifying and weakening host antiviral defenses. . Hepatocellular carcinoma (HCC), the second most common and fastest-growing cause of cancer death worldwide, liver fibrosis, cirrhosis, and other conditions are all greatly increased by viral hepatitis(7). According to estimates, 170 million people worldwide have chronic HCV infection, and 3–4 million new cases arise each year (8).

The complex antigen on the surface of HBV called HBs Ag served as the basis for the diagnosis in our study. When HBs Ag is found in serum or plasma, it means that the hepatitis B infection is active. While the presence of HCV antibody (HCVAb) in serum or plasma samples was detected in HCV infection, symptoms or jaundice will not be seen for 3 to 5 weeks (9). Acute HBV infection stimulates CD4+ and CD8+ T cell responses, as well as increased interferon-gamma production (IFN-). IFN is an important cytokine in virus clearance and the control of HBV infection (10) As a result of this activation, inflammatory cytokines like interleukin (IL)-1 and IL-18 mature and are released (11). A cytokine belonging to the IL1 family is IL18. Its primary function, which originally went by the name of IFNg-inducing factor, is to promot the production of Interferon -gamma by a variety of immune system cell, mainly Th1 CD4 T cells and NK cells, regularly in conjunction with IL 12. There are other cells that produce IL18 besides macrophages, epithelial cells and dendritic cell. The inflammasome regulates the functional production of this peptide through transcriptional regulation and also proteolytic enzymes modification of its synthesized peptide. Serum levels of IL-18 are increased in patient with chronic hepatitis B virus, hepatitis C virus, and hepatocellular carcinoma(HCC) ,the higher levels of circulating IL-18 are related with a worse prognosis for hepatocellular carcinoma (12).

Patients and control

This study included 60 patients who were infected with hepatitis B and C. This research was conducted from February to May 2022. Following ethical approval, the investigation was carried out at the General ALFalloja Hospital and public health laboratory in Al-Anbar province The study participants were classified as follows:

- Group I consists of 30 patients (males and females) with the infective stage of hepatitis B (HBsAg) positive (24)case and hepatitis C (HCV Ab)positive (6) case, ranging in age from (21-56) years
- Group II consists of 30 patients (males and females) hepatitis B (HBV)

HBsAg negative and hepatitis C (HCV Ab) negative, ranging in age from (21-61) years. These healthy volunteers with no clinical or laboratory evidence of liver disease. Patients' sera were also tested for alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total serum bilirubin (TSB). Additionally, a control sample of 30 healthy male and female blood donors was used.

Laboratory methods

Three enzyme-linked immunosorbent assay (ELISA) kits were used for qualitative assessments of anti-HBV antibodies in sera of patients and control (anti-HBc IgM, -HBc IgG and -HbsAg antibodies). The kits were products of MyBioSource Company (USA). Serum level of IL-18 was determined using a kit produced by Abbexa Ltd (Cambridge, UK). The kit was based on a sandwich ELISA technology. Standard procedures recommended by the manufacturers were followed in these assessments.

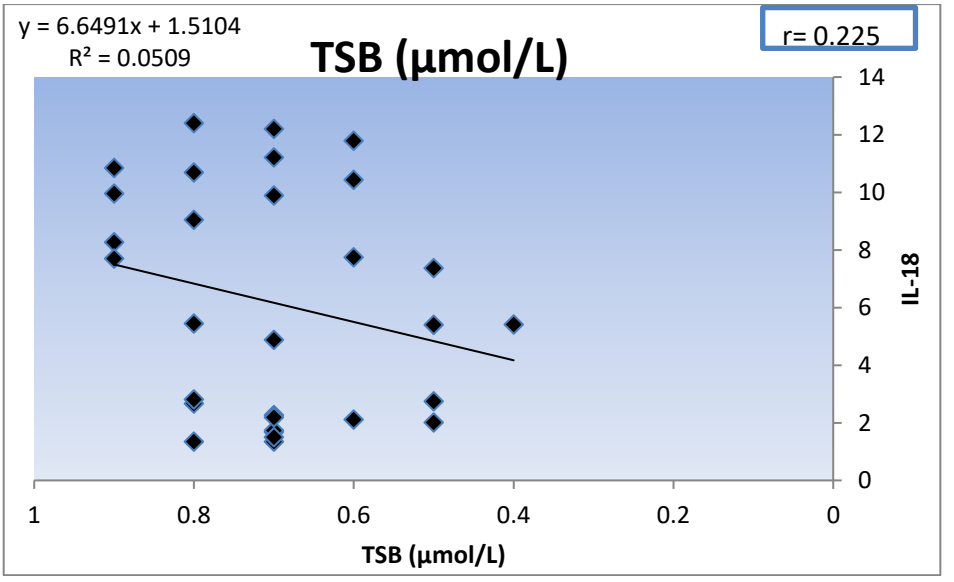
Statistical analysis

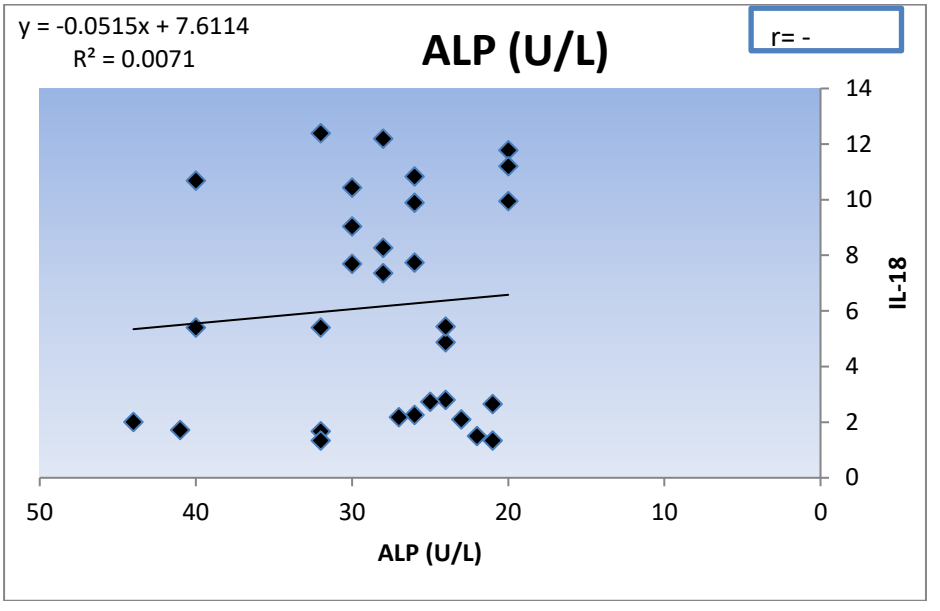
Data analysis using the T-test under the 0.05 level, the running test test 1.05, the analysis test using the SPSS statistical program, as well as the hosting with an Excel program to display the results (13)(14)

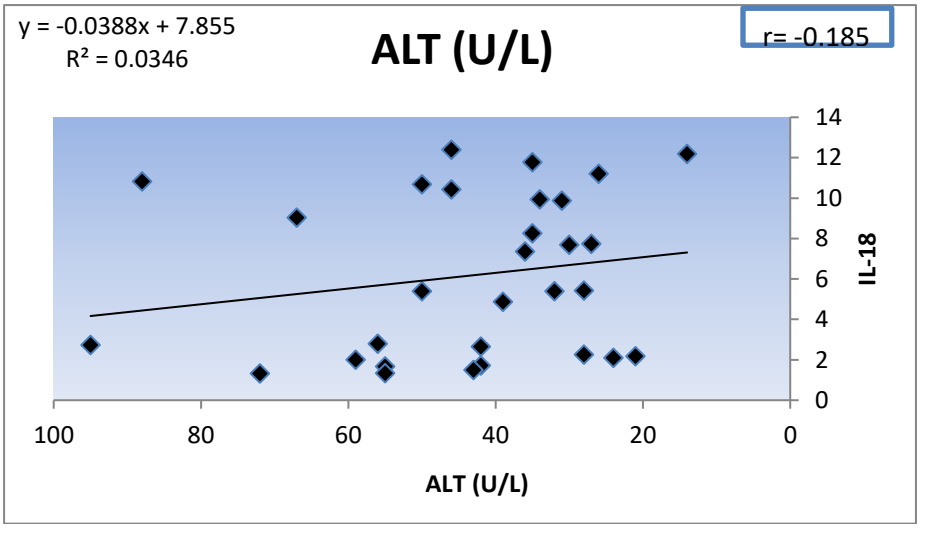
$$\mathbf{r} = \frac{\sum xi\ yi - \frac{(\sum xi)(\sum yi)}{n}}{\sqrt{(\sum x^2 i - \frac{(\sum xi)^2}{n})(\sum y^2 i - \frac{(\sum yi)^2}{n})}}$$

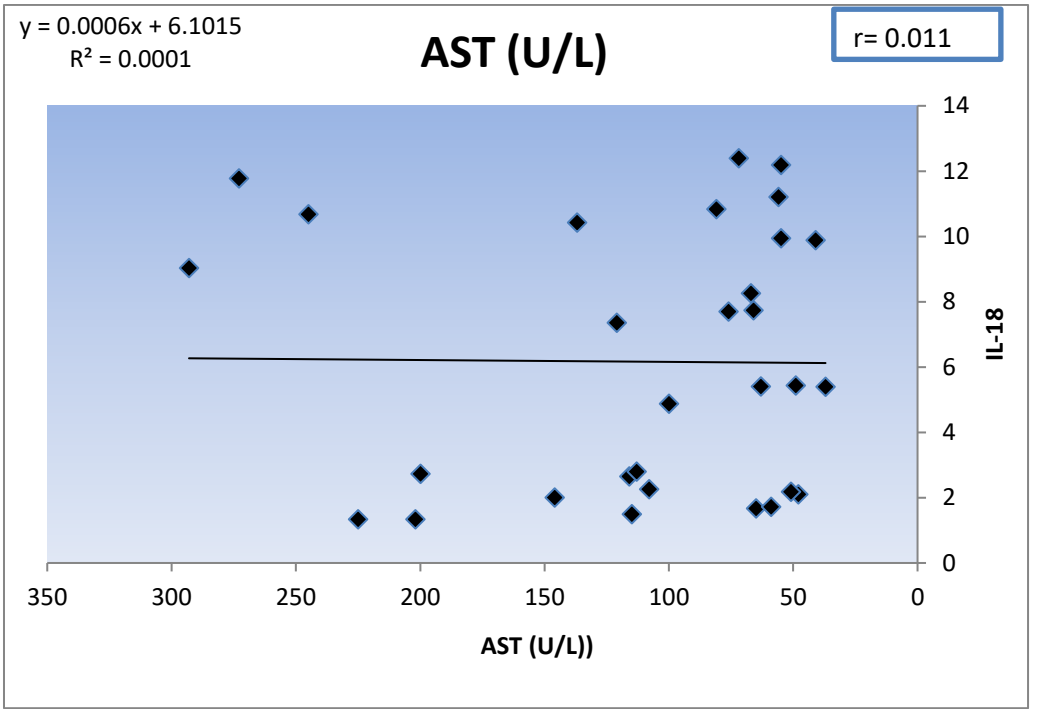
Results and Discussion

Spearman bivariate analysis was employed to assess the correlation between serum level of IL-18 and LFTs. The analysis demonstrated no significant correlations between serum level of IL-18 and LFTs: TSB (r = 0.225), ALP (r = 0.0845), ALT (r = -0.185) and AST (r = - 0.011)




y = -0.0515x + 7.6114
R² = 0.0071
ALP (U/L)
r= -
14
12
10
8
6
4
2
0
IL-18
50
40
30
20
10
0
ALP (U/L)

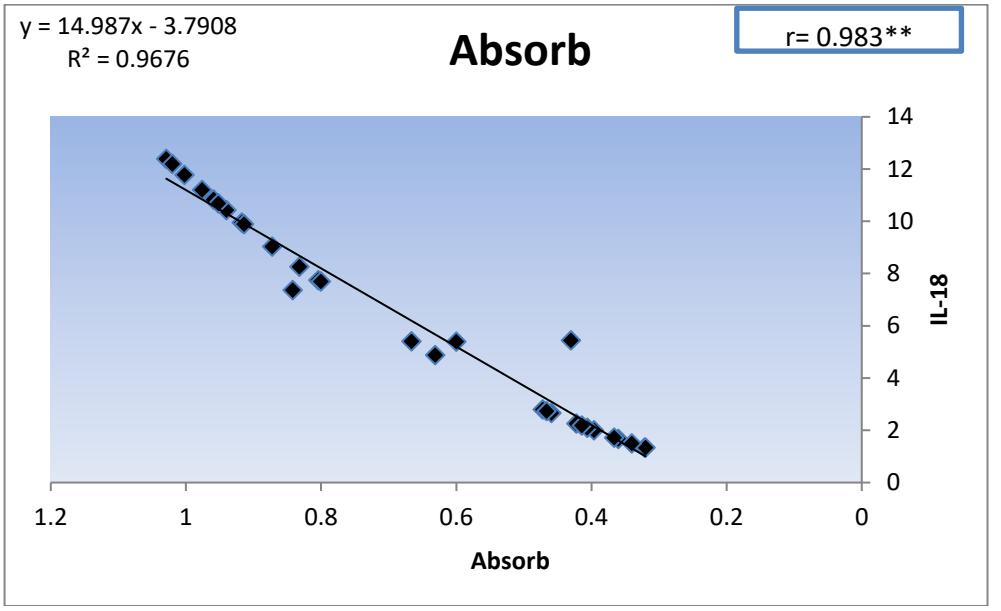

y = -0.0388x + 7.855
R² = 0.0346
ALT (U/L)
r= -0.185
14
12
10
8
6
4
2
0
IL-18
100
80
60
40
20
0
ALT (U/L)



Il -18 described as inducing factor, interleukin (IL)-18 has been reported to be involved in Th1 and Th2 immune responses, as well as in activation of NK cells and macrophages. There is convincing evidence that IL-18 plays an important role in various pathologies inflammatory diseases (15). The correlation between IL-18 and LFTs were analyzed ,according to the study showed that The IL-18 levels in primary biliary cirrhosis increased according to the disease progression, and fell promptly after living-related liver transplantation. Moreover, serum IL-18 levels in primary biliary cirrhosis were correlated with serum bilirubin concentrations and the Risk scores of the Mayo Clinic prognostic model for the disease. The IL-18 levels observed in patients with autoimmune hepatitis were also elevated, and correlated with the activity of the disease According to the same study, it was found that there is no relationship to the enzymes, ALP ALTand AST (16) . And by a recent study conducted at the Thalassima Center in Baghdad, patients infected with HCV have increased IL-18 concentrations, and serum AST in HCV is usually significantly elevated, while ALT is frequently recorded within normal levels. In HCV positive thalassemic patients, serum ALP is unlikely to be a good predictor of disease progression.(17)

Correlation serum level IL-18 and absorbance of HBV and HCV

In this study, an increase in the level of the concentration of interleukin-18 (IL-18) was observed in the sera of the infected patients in relation to the absorbance of each of the infected samples As in below Figure



These results are consistent with some studies that demonstrate the relationship of hepatitis B virus and hepatitis C virus with increased levels of interleukin-18-IL. Like recent study revealed that the concentration of IL-18 in the sera of HBV and HCV patients was found to be higher than in the controls (18).In chronic hepatitis C and cirrhosis, an increase in the expression of proinflammatory cytokines, in particular IL 18, has been shown, which correlates with IFN-γ production. IL 18 is produced as an inactive precursor, so it needs to be clarified whether IL-18 is present in its active form to exert its effect and induce a Th1 response in hepatitis C infection, and whether IL-18 could be related to disease persistence(19). Another study by Abbate et al. revealed up-regulated expression of the IFN-related genes IFN-γ, IFN-α receptor-1, IFN regulatory factor-1, and IL-18, while expression of IFN-α and IFN-β was significantly lower in patients with HCV infection when compared with non-alcoholic steatohepatitis(20).

Ludwiczek et al. found elevated levels of plasma IL-18 and IL 18 binding protein (IL-18BP) in patients with chronic liver disease compared with healthy controls.(21). While a study on clinical data from 2006 to 2016 demonstrated the relationship between interleukin-18 and hepatitis B infection in Xiangyang Central Hospital in China, where HBV patients were classified into high and low viral load groups, respectively, the study noted a decrease in the level of interleukin-IL- 18 and some other cytokines.(22)

References

1. Abbate, I., Romano, M., Longo, R., Cappiello, G., Lo Iacono, O., Di Marco, V., ... & Capobianchi, M. R. (2003). Endogenous levels of mRNA for IFNs and IFN‐related genes in hepatic biopsies of chronic HCV‐infected and non‐alcoholic steatohepatitis patients. Journal of medical virology, 70(4), 581
2. Abdullah, S. M. (2018). Prevalence of Hepatitis B and C virus infection and their co-relation with hematological and hepatic parameters in subjects

undergoing Premarital Screening in the Jazan Region, Kingdom of Saudi Arabia. Pakistan journal of medical sciences, 34(2), 316.
3. Alsamarai AM, Abdulrazaq G, Fatah A, Alobaidi AHA (2016) Seroprevalence of Hepatitis B Virus in Iraqi Population. J Vaccines Immunol 2016: 102. DOI: 10.29011/2575-789X.000102
4. Boulahtouf, Z.; Virzì, A.; Baumert, T.F.; Verrier, E.R.; Lupberger, J. Signaling Induced by Chronic Viral Hepatitis: Dependence and Consequences. Int. J. Mol. Sci. 2022, 23, 2787
5. Haaland, P. D. (2020). Experimental design in biotechnology. CRC press.
6. Hamid, Z. A., & Hadi, R. A. (2022). The Frequency of Hepatitis C Viral Infections and its Correlation with IL-12 and IL-18 among Major Thalassemic Patients in Baghdad. Egyptian Journal of Chemistry, 65(8), 3-6
7. Jefferies, M., Rauff, B., Rashid, H., Lam, T., & Rafiq, S. (2018). Update on global epidemiology of viral hepatitis and preventive strategies. World journal of clinical cases, 6(13), 589.
8. Jiang, H., Cao, F., Cao, H., Rao, Q., & Yang, Y. (2018). Associations of human leukocyte antigen and interleukin-18 gene polymorphisms with viral load in patients with hepatitis B infection. Medicine, 97(30).
9. Karimi, A., Salimzadeh, L., & Bagheri, N. (2014). Hepatitis B virus genotyping among chronic hepatitis B individuals with resistance to lamivudine in Shahrekord, Iran. Jundishapur Journal of Microbiology, 7(4). https://doi.org/10.5812/jjm.10196
10. Li, Z., Yu, X., Werner, J., Bazhin, A. V., & D'Haese, J. G. (2019). The role of interleukin-18 in pancreatitis and pancreatic cancer. *Cytokine & Growth Factor Reviews*, *50*, 1-12.
11. Ludwiczek, O., Kaser, A., Novick, D., Dinarello, C. A., Rubinstein, M., Vogel, W., & Tilg, H. (2002). Plasma levels of interleukin-18 and interleukin-18 binding protein are elevated in patients with chronic liver disease. Journal of clinical immunology, 22(6), 331-337.
12. Markowitz, G. J., Yang, P., Fu, J., Michelotti, G. A., Chen, R., Sui, J., … Wang, X. F. (2016). Inflammation-dependent IL18 signaling restricts hepatocellular carcinoma growth by enhancing the accumulation and activity of tumor- infiltrating lymphocytes. Cancer Research, 76(8), 2394–2405. https://doi.org/10.1158/0008-5472.CAN-15-1548
13. Maya, R. W., & Mohammed, A. H. ESTIMATION OF IL-18 IN PATIENTS INFECTED WITH HBV AND HCV: CASE CONTROL STUDY
14. Mohsen, R. T., Al-azzawi, R. H., & Ad'hiah, A. H. (2019). Hepatitis B virus genotypes among chronic hepatitis B patients from Baghdad, Iraq and their impact on liver function. *Gene Reports*, *17*, 100548.
15. Mohsen, R. T., Al-azzawi, R. H., & Ad'hiah, A. H. (2020). Serum level of interleukin-35 in patients with chronic hepatitis B virus infection. Iraqi Journal of Science, 61(11), 2860-2865.
16. Mohsen, R. T., Al-azzawi, R. H., & Ad'hiah, A. H. (2020). Single nucleotide polymorphisms of interleukin-35 subunit genes predict host susceptibility to chronic hepatitis B virus infection among Iraqi patients. *Meta Gene*, *25*, 100735.
17. Omar, A. A. A. (2012). The infection with HBV and HCV and their relationship to ABO blood group among blood donors

18. Shakeel HA, Maqsood H, Ali B, Khan AR. Association of chronic viral hepatitis with ABO blood groups and rhesus (Rh) factor. Int J Res Med Sci 2018;6:1114-8.
19. Sharma, A., Chakraborti, A., Das, A., Dhiman, R. K., & Chawla, Y. (2009). Elevation of interleukin‐18 in chronic hepatitis C: implications for hepatitis C virus pathogenesis. *Immunology*, *128*(1pt2), e514-e522
20. Steel, R.G., and J.H.Torrie, 1960. Principle and procedure of statistical. McGraw-hill book company , Inc.new york. Pp481.
21. Suljevic D, Mehinovic L, Alijagic A. Hepatitis and biochemical markers in correlation with alpha-fetoprotein as a diagnostic indicator for the HBV and HCV differentiatn
22. Xie, W. hui, Ding, J., Xie, X. xia, Yang, X. huang, Wu, X. F., Chen, Z. xin, … Li, D. (2020). Hepatitis B virus X protein promotes liver cell pyroptosis under oxidative stress through NLRP3 inflammasome activation. Inflammation Research, 69(7), 683–696. https://doi.org/10.1007/s00011-020-01351-z
23. Yamano, T., Higashi, T., Nouso, K., Nakatsukasa, H., Kariyama, K., Yumoto, E., … & Tsuji, T. (2000). Serum interferon-gamma-inducing factor/IL-18 levels in primary biliary cirrhosis. Clinical & Experimental Immunology, 122(2), 227-231