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ORIGINAL

The role of soluble CD137 in development of liver cirrhosis among hepatitis B virus infected individuals

El papel del CD137 soluble en el desarrollo de cirrosis hepática entre individuos infectados por el virus de la hepatitis B

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ABSTRACT

Introduction: viral and tumor management are mediated by the production of CD137 as a co-receptor for T cells.
Objective: the purpose of the research is to examine the link between soluble CD137 and the development of liver cirrhosis in HBV-infected people.
Method: ninety individuals were recruited. A questionnaire was used to collect age and gender information. The serum quantities of soluble CD137, TNF-α, IFN-γ, IL-6, and IL-10 in the patients were measured using the ELISA technique. Real-Time-PCR was used to calculate the number of HBV DNA copies (viral load). HBV genotypes were determined using PCR, AST, and ALT levels were determined using a Mindary BS 120TM chemical auto-analyzer.
Result: the study found significant positive associations between CD137 levels and TNF-γ (P=0,014/R=0,258) and IFN- (P=0,019/R=0,246), but not with IL-6 (P=0,579/R=0,059). There were no significant negative correlations between soluble CD137 levels and viral load (P=0,495/R=-0,073), IL-10 (P=0,474/R=-0,076), AST (P=0,140/R=-0,157), or ALT (P=0,140/R=-0,111). The highest mean of CD137 was detected in patients with pure genotype D, and the concentration of CD137 dropped as viral load increased.
Conclusions: the considerable positive correlations of soluble CD137 with (TNFα- and IFN-γ) and the positive correlation with (IL-6) along with the negative correlations with viral load, AST, ALT, and IL-10 may indicate that CD137 has a beneficial effect on the prognosis of HBV infection. There was significant influence of a specific HBV genotype on CD137 expression.

Keywords: Soluble CD137; HBV; Liver Cirrhosis; Cytokines.

RESUMEN

Introducción: el manejo de los virus y los tumores está mediado por la producción de CD137 como correceptor de las células T.
Objetivo: el propósito de la investigación es examinar el vínculo entre el CD137 soluble y el desarrollo de cirrosis hepática en personas infectadas por el VHB.
Método: se reclutaron noventa individuos. Se utilizó un cuestionario para recopilar información sobre la edad y el género. Las cantidades séricas de CD137 soluble, TNF-α, IFN-γ, IL-6 e IL-10 en los pacientes se midieron utilizando la técnica ELISA. Se utilizó PCR en tiempo real para calcular el número de copias de ADN del VHB (carga viral). Los genotipos del VHB se determinaron mediante PCR, los niveles de AST y ALT se determinaron utilizando un autoanalizador químico Mindary BS 120TM.
Resultados: el estudio encontró asociaciones positivas significativas entre los niveles de CD137 y TNF-γ (P = 0,014/R = 0,258) e IFN-γ (P = 0,019/R = 0,246), pero no con IL-6 (P = 0,579/R = 0,059). No hubo correlaciones negativas significativas entre los niveles solubles de CD137 y la carga viral (P = 0,495/R = -0,073), IL-10 (P = 0,474/R = -0,076), AST (P = 0,140/R = -0,157) o ALT (P = 0,140/R = -0,111). La media más alta de CD137 se detectó en pacientes con genotipo D puro, y la concentración de CD137 disminuyó a medida que aumentaba la carga viral.
Conclusiones: las correlaciones positivas considerables del CD137 soluble con (TNFα- e IFN-γ) y la correlación positiva con (IL-6) junto con las correlaciones negativas con la carga viral, AST, ALT e IL-10 pueden indicar que el CD137 tiene un efecto beneficioso en el pronóstico de la infección por VHB. Se observó una influencia significativa de un genotipo específico del VHB en la expresión del CD137.

Palabras clave: CD137 Soluble; VHB; Cirrosis Hepática; Citocinas.

INTRODUCTION

In order to remove and clear the virus, the immune system deals with HBV through a variety of ways. This can be humoral with specific antibodies or cell-mediated immunity, particularly cytotoxic T cells that rid the liver of HBV replicative intermediates by secreting type 1 inflammatory cytokines, restricting the virus's dissemination to healthy cells and decreasing the level of immune-pathology needed to end the infection.[1] Chronic hepatitis, liver cirrhosis, and hepatocellular cancer are all outcomes of persistent hepatitis B virus infection.[2] Infection persistence was directly connected to a lack of or inactivity CD4+ and CD8+ T cells. [1] T lymphocyte co-stimulation is required for proper stimulation and subsequent activity because T cell activation without co-stimulation generates energy, and subsequent stimulation reduces T cell responsiveness. As a result, T cell activation needs two types of signals: a main signal and many co-signals of co-stimulation.[3]

CD137 ligand (CD137L or 4-1BBL) is a type II membrane glycoprotein with a car-boxy-terminal extracellular domain of 34 kD that is encoded on mouse chromosome 17 and human chromosome 19.[4] The presence of CD 137 on the surface of immune cells is stimulated and shows up on active CD4+ T cells, CD8+ T cells, dendritic cells, and acti-vated Natural Killer (NK) cells in addition to expression on blood vessel endothelial cells, CD4+CD25+ regulatory T cells, and other immune cells, while CD137 ligand is expressed more frequently on antigen presenting cells such as dendrtitc cells, activated B cells, and macrophages than T cells.[5, 6]

T cell activation via CD137 as a co-stimulatory signal induces T cell proliferation, boosts interferon gamma production, and reduces stimulation-induced mortality of ef-fector T cells, all of which improve protection against viral infection. [7] Because it pro-motes CD137 signaling and boosts the responsiveness of intra-hepatic HBV-specific T cells, incubating intra-hepatic T cells with CD137L and anti-programmed death ligand 1 (ant-PD-L1) improved their responses to HBV.[8]

Another investigation on the role of CD137 in antigen independent memory T cell stimulation indicated that CD137 activation may excite HBV-nonspecific memory T cells, resulting in persistent inflammation and the pathogenesis of liver disorders.[9] CD137L expression on monocytes in chronic hepatitis B patients is linked to liver cirrhosis.[10] Liver cirrhosis is a major consequence of chronic HBV infection, driven by persistent viral replication, immune-mediated liver injury, and fibrosis. The goal of this study is to determine the relationship between soluble CD137 and the development of liver cirrhosis in HBV- infected individuals.

METHOD

It was a prospective cross sectional study conducted in Ibn Sina specialized hospital and Alzaiem Alazhari University at Khartoum State, Sudan, for a duration of between February 2022 and January 2023.

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Sample size

A total of 90 patients were recruited to participate in this study, the age range was between 18 and 75 years old (Mean age 41,7 years). The study included patients who were positive for HBV infection, indicated by being positive for HBsAg using ELISA.

All of the subjects tested positive for HBV, as indicated by HBsAg. The participants were split into two groups. Thirty people with hepatic cirrhosis were enrolled in one group. The second group consisted of 60 HBV-positive participants who did not have liver cirrhosis. The final group consisted of 30 HBV carriers, 19 acute hepatitis patients, and 11 newly diagnosed HBV patients.

The ethical considerations and individual conformance in this study were taken into account by the approval of the Ethical committees of Alzaiem Alazhari University and Ibn Sina specialized hospital (AA/EC/2021-11/134), as well as the use of written agreements within the questionnaire and signed by the participants.

Inclusion criteria

Patients infected with HBV with complications, mainly liver cirrhosis and/or hepatocellular carcinoma (HCC).[11]

An ultrasound scan is still used to identify HCC and can detect extremely small lesions within the liver. Magnetic resonance imaging with multiphase contrast enhancement has been used in more recent practice. At some hospitals, magnetic resonance imaging has become the preferred diagnostic method for HCC. HCC is often hypointense on T-1-weighted imaging and hyperintense on T-2-weighted images; however, there is considerable diversity in its appearance that may be due to bleeding foci, copper buildup, glycogen accumulation, or areas of fatty alteration.[12]

Exclusion criteria

Patients with other liver diseases have been excluded.

To detect HBsAg, an ELISA kit was utilized, and the regeant was obtained from Fortress Diagnostics (www.fortressdiagnostics.com). Also, an ELISA kit for soluble CD137 was obtained from bpro® in Nanjing, China. IFN-, TNF-, IL-6, and IL-10 were purchased from abcam® (www.abcam.com), and HBV DNA extraction was performed using the G-spinTM Total DNA Extraction Kit from (iNtRON Biotechnology Incorporation®). Sansure biotech inc (www.sansureglobal.com) provided the HBV viral load (real time PCR). HBV genotypes, on the other hand, were identified by PCR using particular primers in plate 1.[12] Pharmacia Biotech® DNA ladder.

Primer	Sequence (5′-3′)	Nucleotide Position	Specificity
P1 (sense)	TCA CCA TAT TCT TGG GAA CAA GA	2817–2839	Common
S1-2 (antisense)	CGA ACC ACT GAA CAA ATG GC	704–684	Common
B2 (sense)	GGC TCM AGT TCM GGA ACA GT	67–86	types A–E
BA1R (antisense)	CTC GCG GAG ATT GAC GAG ATG T	113–134	type A
BB1R (antisense)	CAG GTT GGT GAG TGA CTG GAG A	324–345	type B
BC1R (antisense)	GGT CCT AGG AAT CCT GAT GTT G	165–186	type C
BD1 (sense)	GCC AAC AAG GTA GGA GCT	2979–2996	type D
BE1 (sense)	CAC CAG AAA TCC AGA TTG GGA CCA	2955–2978	type E
BF1 (sense)	GYT ACG GTC CAG GGT TCA CA	3032–3051	type F
B2R (antisense)	GGA GGC GGA TYT GCT GGC AA	3078–3097	types D–F

Plate 1. Specific primers sequences use for HBV genotypes[12]

Data analysis

Statistical tests were conducted through the windows package of SPSS software, version 21 (SPSS

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Inc, Chicago, IL),. The Pearson correlations, ANOVA, and means of the tested parameters were calculated, confidence interval at the 95 % level, and P<0,05 was the accepted significance level.

RESULTS

CD137

The mean blood level of CD137 was higher (P 0,016) among HBV positive people who weren't suffering from liver cirrhosis (92 ±200) pg/ml versus those who were diagnosed with liver cirrhosis (62 ±106) (figure 1). Figure 2 displays means of soluble CD137 among study groups.

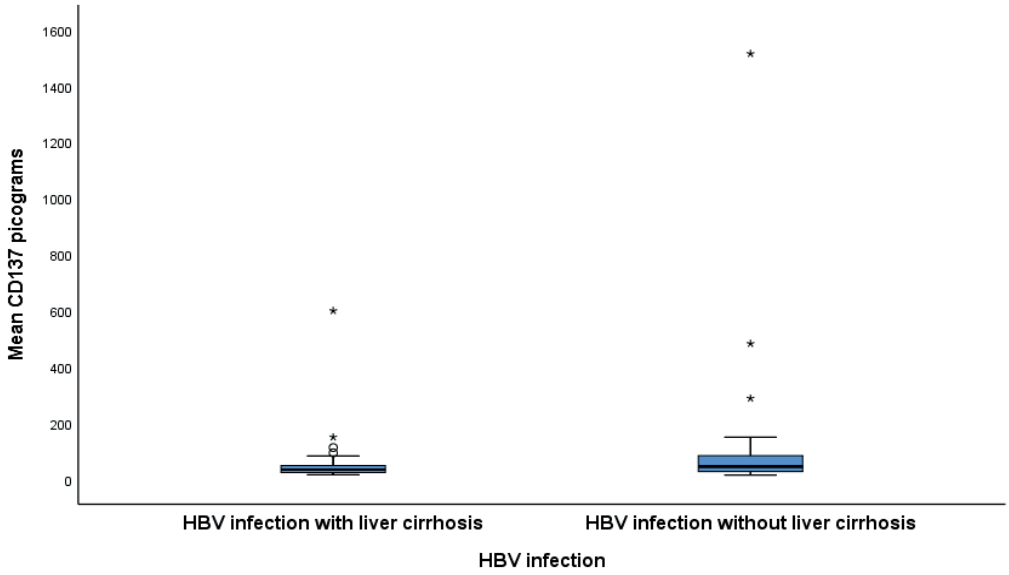

Figure 1. Comparison of the mean serum level of CD137 among study population.

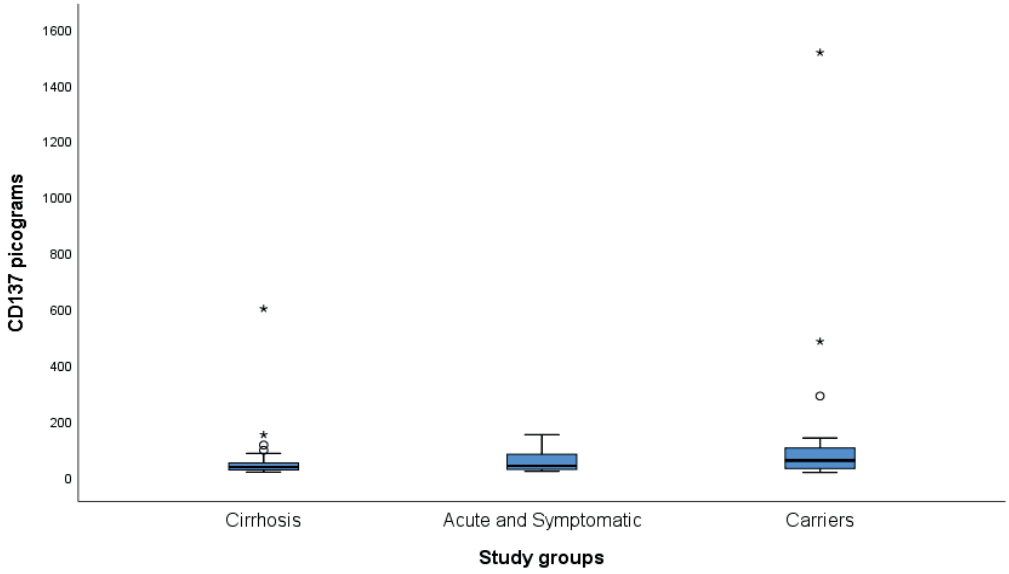

Figure 2. Comparison between means of soluble CD137 in study groups according to symptoms

1. *Correlation between CD137 and HBV viral load*

There was a negative correlation between the concentration of soluble CD137 and viral load among the overall study population (P 0,495/R -0,073) and with subgroups of recent HBV infection (P 0,210/R -0,410), acute hepatitis B (P 0,182/R -0,320) and HBV infection with liver cirrhosis (P 0,639/R -0,089), but no correlation with HBV carriers (P 0,984/R0,004). (Figure 3, 4).

The differences did not reach statistical significance among the groups with a higher viral load. HBV with liver cirrhosis and no correlation among HBV carriers group, which includes the lowest concentration of viral load. These findings may give a clue to the positive effect of CD137 on controlling HBV replications.

This study showed a significant positive correlation between the concentration of soluble CD137 and TNF-α among all study populations (P 0.014/R 0.258) and among the HBV carrier subgroup (P 0,011/R 0,459). The

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correlation in the recent HBV infection group (P 0,301/R 0,344), and negative with acute hepatitis B (P 0,612/R -0,124), and HBV with liver cirrhosis (P 0,597/R -0,101) (figure 3, 4).

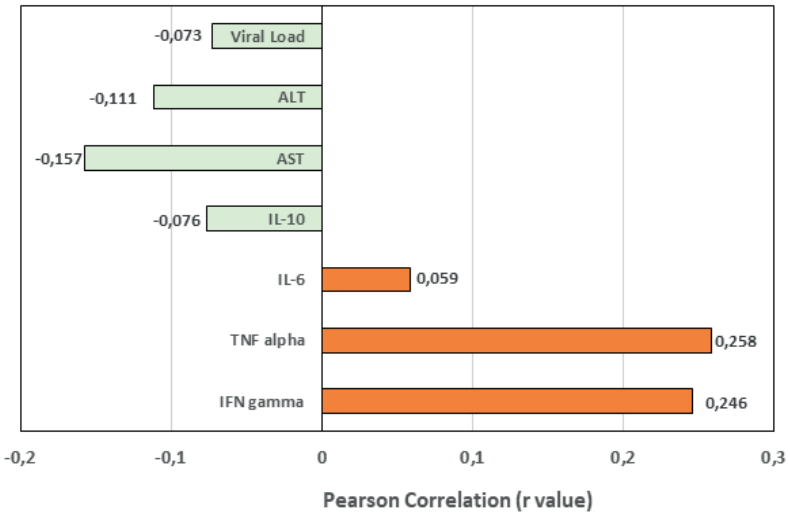

Figure 3. Correlations of CD137 pg/ml with viral load copy/ml, IFN-γ pg/ml, TNF-α pg/ml, IL-6 pg/ml, IL-10 pg/ml, AST IU/Land ALT IU/L among all study populations.

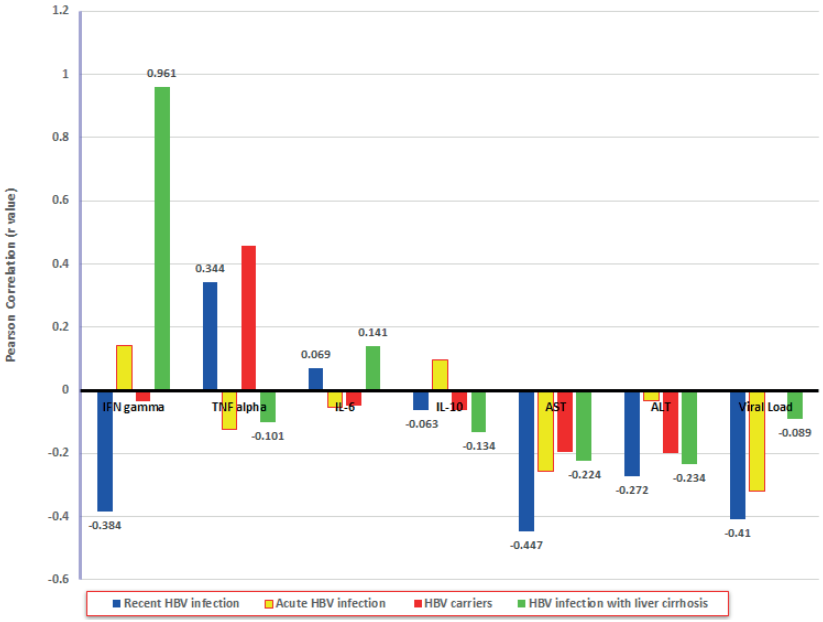

Figure 4. Correlations of CD137ng/ml with viral load copy/ml, INF-γ pg/ml, TNF-α pg/ml, IL-6 pg/ml, IL-10 pg/ml, AST IU/L and ALT IU/L among subgroups of study population.

2. *Correlation between CD137 and Cytokines*

The study found a significant positive correlation between soluble CD137 concentration and INF-γ and liver cirrhosis in all study populations. The correlation was insignificant in acute hepatitis B and insignificantly negative with recent infections and carriers. Insignificant positive correlations were found with IL-6, IL-6, IL-10, AST, and ALT. No significant negative correlation was found with acute hepatitis (figure 3, 4).

3. *Association between CD137 and HBV genotypes*

In the distribution of soluble CD137 among different HBV genotypes, the highest mean was found in pure genotype D (0,10304), followed by genotype A+B+D (0,08930), A+D (0,08235), B+D (0,06867), B (0,05087), A (0,02525) and A+B+E (0,02196).

This indicates that, the genotype D showed highest concentration of soluble CD137, regardless of whether it was a single genotype or mixed with other genotypes (figure 5).

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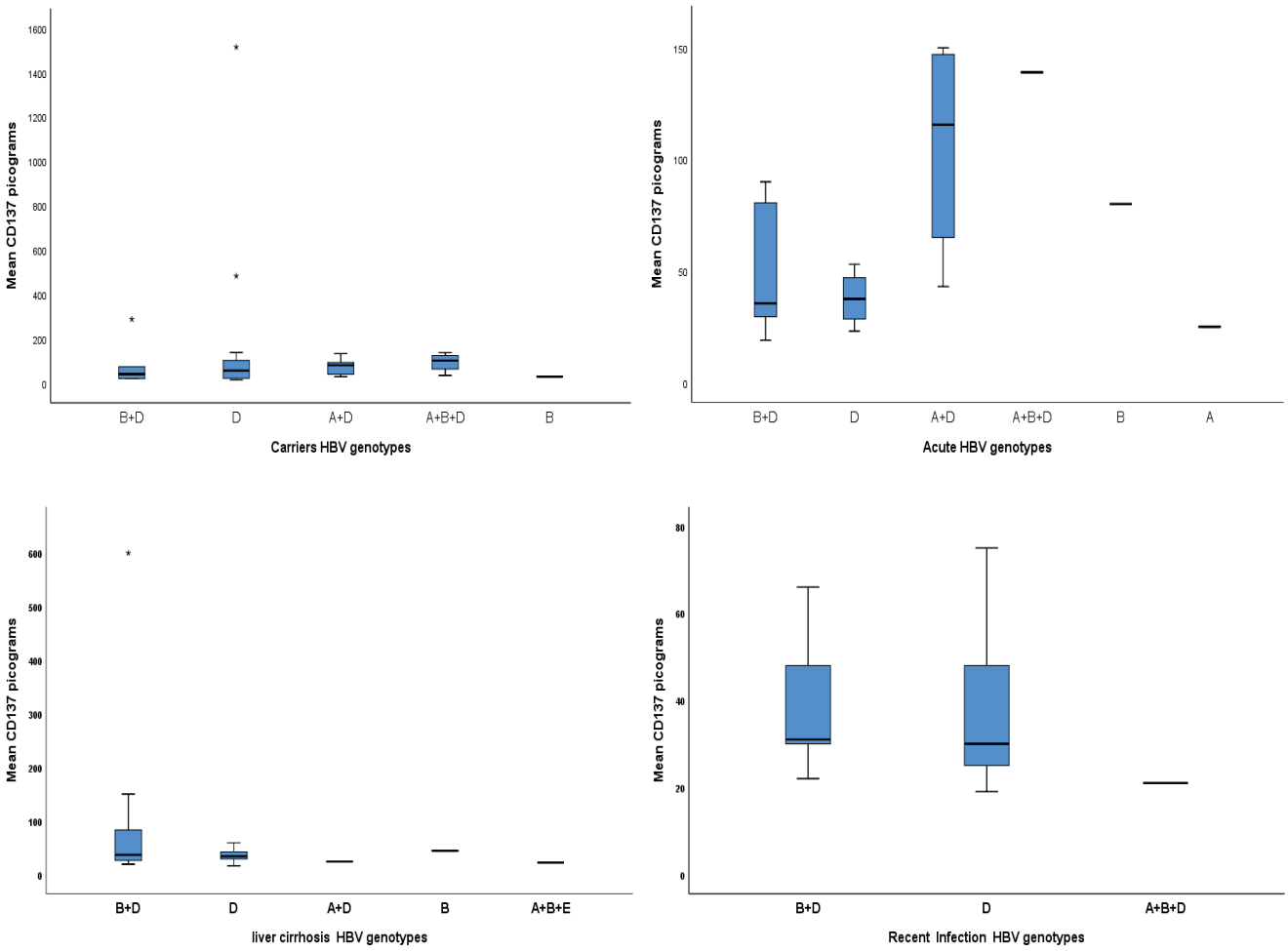

Figure 5. The comparisons between CD137 ng/ml within different HBV genotypes among study populations

Figure 5 shows the statistics of study variables among the cirrhosis group of the study population: the genotype B+D showed the highest concentration of CD137, genotype D showed the highest viral load, genotype B+D showed the highest INF gamma level, genotype A+D showed the highest TNF alpha concentration, genotype B showed the highest IL-6, genotype D showed the highest level of IL-10 concentration, genotype D showed the highest concentration of AST, and genotype D showed the highest level of ALT.

4- Comparison of CD137 level with viral loads

Soluble CD137 concentration decreases with viral load, with varying concentrations observed among individuals with different viral loads. (Figure 6).

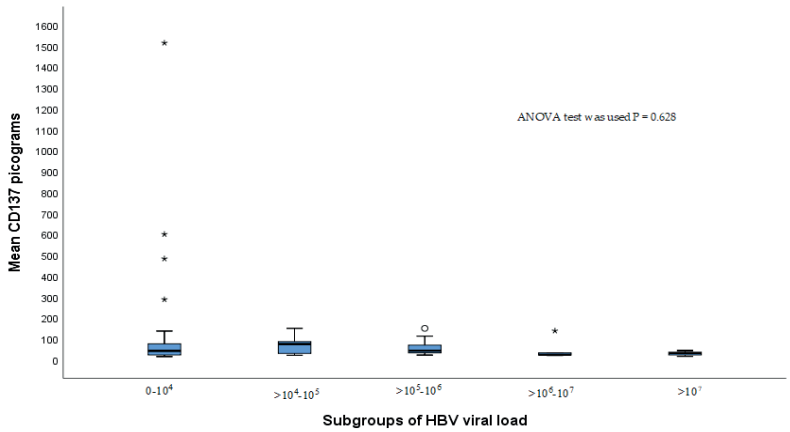

Figure 6. Comparison of mean serum levels of CD137 among subgroups of HBV viral load.

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DISCUSSION

The present study shows a difference between the means of soluble CD137 among different groups of the study population, with a marked increase among HBV carriers, then acute HBV infected, HBV infected with liver cirrhosis, and recent HBV infected patients. Also, this study shows an increase in CD137 in all HBV- infected without complications of liver cirrhosis in comparison with HBV- infected with liver cirrhosis.

There were few published data supporting this work, but generally, several studies were done and concluded the positive role of CD137 in the pathogenesis of HBV. Myers et al. demonstrated that activating T cells with the help of CD137 as a co-stimulator improves immunity against viral infection because it induces T cell proliferation, increases interferon gamma production, and prevents activation-induced death of effector T cells.[7] Furthermore, incubating intra-hepatic T cells with CD137L and anti-programmed death ligand 1 (ant-PD-L1) boosted their responses to HBV, indicating activated CD137 signaling increases the responses of intra-hepatic HBV-specific T cells.[8,13]

On the contrary, Another study on the role of CD137 in antigen independent stimulation of memory T cells was conducted by Zhu et al. and they concluded that CD137 stimulation may stimulate HBV-nonspecific memory T cells, leading to chronic inflammation and the pathogenesis of liver diseases,[9] and the expression of CD137L monocytes in chronic hepatitis B patients is closely associated with liver cirrhosis.[10, 11, 12]

On the other hand, CD137 activation prevents tumor recurrence and metastasis in cancer patients,[14] and the use of an agonistic anti-CD137 monoclonal antibody has been found to have an anti- HCC effect and is considered a promising therapeutic strategy for anti-tumor immunity stimulation against HCC.[15] Chester et al. reported a similar conclusion, stating that CD137 agonists may become part of essential anticancer combination medicines in the future since they expedite cancer immunotherapy.[16]

This study shows a significant positive correlation between the concentration of soluble CD137 and TNF-α among all study populations and among the HBV carrier subgroup. There was a correlation in the recent HBV infection group and a negative with acute HBV infection and HBV infection with liver cirrhosis.

The current investigation found a substantial positive connection between serum concentrations of soluble CD137 and INF-γ in all study populations (including among HBV infection subgroups with liver cirrhosis). The connection was non-significant in the acutely HBV- infected group and non-significant in the recent HBV infection and HBV carriers.

There were few published data regarding the correlation of soluble CD137 with HBV viral load, IFN-γ, TNF-α, IL-6, IL-10, AST, and ALT among HBV patients such as IFNs modify the environment of the immune system to organize diverse immune cells, according to Borden. Macrophages, natural killer cells, dendritic cells (DCs), and T cells were all activated by IFNs. All of these activated immune cells release cytokines like IL-1, IL-6, TNF- α, and IFN-γ. Among these, IFN-/ partly stimulated IL-6, IL-12, and IL-15 production by DCs, which then altered B and T cell differentiation (Th1 polarization) and activation.[17, 18] Our findings imply that CD137 has a positive prognostic effect in the pathogenesis of HBV infection since the concentration showed a substantial positive connection with inflammatory and protective cytokines (INF- γ and TNF- α) but not with IL-6. Whereas demonstrated a weak negative connection with viral load, which is directly related to HBV viremia, IL-10, an inhibitory cytokine, and the liver enzymes AST and ALT, which suggest liver damage. This could indicate that CD137 has a positive influence on prognosis and symptom control.[19, 20, 21, 22]

This study illustrates that the concentrations of CD137were increased among HBV patients with normal AST and ALT in comparisons to patients with abnormal AST and ALT in all study population. Also the concentration of soluble CD137 was decreased with increase of the viral load.

This finding may indicate the positive prognostic effect of CD137 in controlling both the viral load and symptoms of HBV infection.

A study conducted by Segal et al. indicated that activation of CD137 prevented tumor recurrence and metastasis in cancer patients.[14] Furthermore, the anti-HCC activity of agonistic anti-CD137 monoclonal antibody has been discovered to be a viable therapeutic method for anti-tumor immune promotion against HCC.[15] Moreover, because it enhances cancer immunotherapy, the CD137 agonist may become part of crucial anticancer combination medicines in the future.[16, 23]

CONCLUSION

The decrease in soluble CD137 concentration among cirrhosis patients more than non-cirrhosis patients may suggest the role of CD137 as protective against cirrhosis. The elevated level of CD137 among HBV carriers' subgroup may indicate the role of CD137 in maintaining carrier status and preventing the bad prognosis of HBV infection. The soluble CD137 showed significant positive correlations with TNF-α and INF-γ, positive correlation with IL-6, and negative correlations with viral load, IL-10, AST, and ALT.

RECOMMENDATIONS

Based on the findings of this study, it has been recommended that CD137 be used a biomarker for the diagnosis of HBV complication and prognosis. Further studies to determine the genotype of HBV and its relation

to the pathogenesis, immune response, and response to chemotherapy are needed.

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CONFLICT OF INTEREST

Author declared that there is no conflict of interest in this research.

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