

Study the alternative immunological parameters of immune cells (sCD14 and sCD163) in patients with chronic viral hepatitis B and C without treatment

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ABSTRACT

Soluble Cluster of Differentiation 14(sCD14) and soluble Cluster of Differentiation 163(sCD163) are the circulating forms of the cell surface receptors CD14 and CD163 expressed on the surface of monocytes and macrophages. When these cells become activated, the extracellular domains of the CD14 and CD163 receptors are shed or cleaved from the cell surface, releasing the soluble forms in the circulation, which are considered valuable biomarkers for evaluating inflammatory conditions. The sCD14 and sCD163 are both done by ELISA technique which showed a significant difference between the patient and control groups, where these parameters increased in the patient groups compared to the control group, sCD14(ng/ml) was in the HBV group (44.2±7.9), the HCV group (46.8±8.9) and healthy group (35.1 ± 6.5), while sCD163(ng/ml) was in the HBV group (106.8±9.4), the HCV group(104.3±3.3), and healthy group (93.01±5.9), the P value was < 0.000 for both parameters. Receiver Operating Characteristic (ROC) analysis shows that it can distinguish patient from control. It was performed by using the serum levels of each sCD14 and sCD163 in patients with (HBV and HCV) and a healthy control group according to the presence of the disease. The diagnostic performance of these soluble biomarkers was evaluated in the two patient groups (HBV and HCV) by using ROC analysis, and sCD163 showed a higher diagnostic performance compared to sCD14, where was the area under the curve in the HBV group 0.96 vs 0.83 while in HCV group 0.97 vs. 0.86 respectively, with statistically significant differences (P=0.000). In conclusion, the results of this study demonstrate that sCD163 is a more useful and reliable biomarker for predicting and differentiating HBV and HCV infection compared to sCD14, and sCD163 could be a valuable non-invasive tool for the clinical management of viral hepatitis. infection compared to sCD14, and sCD163 could be a valuable non-invasive tool for the clinical management of viral hepatitis.

Keywords: HBV; sCD14; sCD163

INTRODUCTION

Hepatitis B and C viruses are of great importance because of their impact on public health and their high probability of developing into a chronic infection, which leads to severe consequences such as carcinogenesis and fibrosis of liver cells and thus may lead to death ¹.



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2. The immune response against liver viruses, in general, is an immune response that includes both types (innate and adaptive) separately and through their interaction. As is known, the immune response begins with the first line of defense represented by innate immunity through its receptors, which are known as pathogen recognition receptors (PRRs), through their recognition of viral pathogen-associated molecular patterns (PAMPs). Viral DNA is the main PAMP that different PRRs can recognize^{3, 4}. In addition, humoral and cellular immunity plays an essential role in the response against these viruses^{5, 6, 7}. Chronic viral infections are characterized by persistent inflammation and tissue damage. Monocyte and macrophage cells have a multifaceted role in determining the course of the disease depending on the viral strategies that manipulate macrophage activation patterns (classical activation of M1, alternative activation of M2) through the signaling molecules they produce. Monocyte/macrophage cells have many markers on their surface, the most important of which are CD14, CD64, CD80, CD86, CD163, etc., as these markers increase with other inflammatory markers when infected with many diseases^{8, 9}, and CD14 and CD163 are chief distinctive markers for these cells. The soluble clusters of differentiation (sCD) are alternative markers for these immune cells, depending on their source, so¹⁰ Yap and colleagues 2023 indicated in their review that sCD163 is increased in acute and chronic inflammatory diseases, while sCD14 shed during the inflammatory process due to infection are considered promising biomarkers of monocyte-macrophage activation^{11, 12}. Many studies have indicated the role of these immune markers (sCD14 and sCD163) and their increase in viral infections such as HIV, measles, COVID-19, and other viruses^{13, 14, 15}, which indicates the continuous activation of these cells. As mentioned, monocytes and macrophages are essential in the immunopathology of many viruses' infections. The present study analyzed the levels of these immune markers (sCD14 and sCD163), which give us an idea about the activation of these cells in untreated chronic viral hepatitis type B and C patients, aim of the study: This study aims to compare the levels of sCD14 and sCD163 among three groups: viral hepatitis groups (HBV & HCV) and the healthy control group, in addition to evaluating the diagnostic performance of these two biomarkers in distinguishing between patients from the healthy control group through the use of ROC analysis.

METHOD:

Subjects and sampling

The total number of samples collected was 262, distributed among patients, with 222 samples infected with hepatitis B and C viruses distributed as follows: HBV103 (64 male and 39 female) and HCV 119 (male 64 and female 55) were collected from the Hepatology and Gastroenterology Teaching Hospital in the Medical City/Baghdad governorate from July 2023 to January 2024. The one hundred

samples were selected from all patients with viral hepatitis B or C who did not use any treatment for this disease and had viral load results. Samples were excluded from viral hepatitis patients pregnant women, children, the elderly, and who have other diseases such as kidney failure and thalassemia. The control group had 40 members, and 30 of them were selected based on the negative serological tests and the results of liver function tests within the normal range, in addition to the fact that they were in good health and had no other disease symptoms and were equivalent to the group of patients in terms of age, as their ages ranged from 18 to 58 years. Patients and subjects of the control group were dealt with according to the ethics of scientific research by speaking with them to collect information about the nature of their health and disease, the symptoms, and the duration of the disease, obtaining verbal and informed consent from all participants under the Helsinki Declaration and the approval of the College of Science, Al-Mustansiriyah University (Ref.:BCSMU/0823/0004B). A sufficient amount of blood was drawn to conduct tests for the current study after conversion by centrifuge at 4000 r.p.m for 10 minutes into serum.

Diagnostic serological tests

The serological tests necessary to diagnose patients, included (Anti-HCV by Bio-Tech/Hong Kong for HCV patients), total hepatitis B core antibody (Anti-HBc), (B surface antigen (HBsAg) / by Bio-Tech company/ Hong Kong, total hepatitis B core antibody (Anti-HBc) and (Anti-HBc IgM) by InTec company/ China for HBV patients).

TaqMan Real Time-qPCR detection of viral hepatitis B and C

A viral load test kit (HBV-DNA level and HCV- RNA level detection/COBAS®AmpliPrep/COBAS TaqMan® Quantitative) following the protocols (Roche Amplicor) was done.

Biochemical tests

Finally, liver function parameters were estimated using special tests, which included the following kits (Alkaline phosphatase (ALP), aspartate transaminase (AST), Alanine aminotransferase ALT, Albumin (ALB), total protein (TP), Total Bilirubin (TBIL) by a Semi Auto Clinical Chemistry Analyzer Mindray BA-88A (Shenzhen Bio-Medical Electronics Co., Ltd., China) for all samples in the study.

Determination of serum sCD14 and sCD163 by ELISA

According to the instructions of the manufacturer of the kits used to measure the quantitative concentrations of sCD14 and sCD163, namely Elabscience® Human sCD14 (Catalog No: E-EL-H6149) and Elabscience® Human sCD163 (Catalog No: E-EL-H0036) USA ELISA Kits.

Statistical analysis

Data are normally distributed and presented as mean \pm SD. Differences between multiple groups were compared using a One-Way ANOVA Calculator for Independent Measures test with Tukey's HSD (honestly significant difference) procedure, which facilitates pairwise comparisons. The Receiver operating characteristic (ROC) curve analysis was performed to determine whether serum sCD14 and sCD163 levels were biomarkers of immune response in both hepatitis B and C patient groups by using SPSS software version 20.

RESULTS

The selection of members of the control group was in parallel with the ages of the patient group members. Therefore, we did not find a clear significant difference between the means of age between the three groups, as shown in the table below (1). Serological tests were used as the initial diagnosis of infection with these viruses in the three groups, which was confirmed using a viral load test for both viruses (B and C) in the patient groups, where HBsAg, Anti-HBc, anti-HBc IgM, and anti-HCV were used. The results showed a negative for the control group. In contrast, in the HBV patient group, it was positive for HBsAg and Anti-HBc and negative for anti-HBc IgM and anti-HCV, the HCV patient group was negative for HBsAg, Anti-HBc, and anti-HBc IgM, while positive for Anti HCV. The viral load test is a confirmed diagnostic indicator for the presence of the virus infection and is a quantitative indicator of infection table (1) shows the average viral load for HBV was 473039.3 ± 2680307.1 while the viral load average for HCV was 1475834.6 ± 2321514.04 . Biochemical tests showed that there was a significant difference between the three groups in each of the AST, ALT, and ALP tests, and on the contrary, ALB, TP, and TBIL did not show a significant difference Table(1).

Table 1. demographic information examined for the study's participant groups.

	Control	HBV	HCV	P-value
Age(years) Mean±SD	35.8 ± 10.8	35.06±9.93	40.4±9.31	0.07
Viral load (IU/ml) Mean±SD	_____	473039.3±2680307.1	1475834.6±2321514.04	_____
AST(U/L) Mean±SD	19.59 ± 7.87	21.65±8.4	50.8±60.9	0.003
ALT (U/L) Mean±SD	35.82±38.1	11.54 ± 7.5	15.24±10.6	0.0005
ALP (U/L) Mean±SD	188.5 ± 69.8	203.4 ±64.3	303.94±150.50	0.00096
ALB (g/dl) Mean±SD	4.03 ± 0.42	4.02±0.6	3.92±0.6	0.714
TP (g/dl) Mean±SDn	5.2 ± 0.41	5.5 ±0.9	5.4 ±1.04	0.5
TBIL(mg/dL) Mean±SD	0.69 ± 0.22	0.64±0.6	0.8±0.8	0.53

AST (Aspartate aminotransferase), ALT (Alanine aminotransferase), ALP (alkaline phosphatase), ALB (Albumin), TP (Total protein), and TBIL (Total Bilirubin). Soluble CD14 results showed a significant difference between the three groups (P-value is <0.00001), which is due to the low concentration of sCD14 in the sera of the healthy group (35.1 ± 6.5). In comparison, it increased in the two groups of patients, where it was in the HBV group (44.2 ± 7.9) and the HCV group (46.8 ± 8.9), while the sCD163 between the three groups showed a significant difference, as its level in the two patient groups (B and C) was higher than in the control group (106.8 ± 9.4 , 104.3 ± 3.3 , 93.01 ± 5.9) respectively. The Tukey test, which facilitates pairwise comparisons, was used to determine the significant differences between the two groups. It was found that there was a significant difference between the control group and both HBV and HC, respectively. Still, there was no significant

difference between the two groups of patients in the two parameters, as shown in Table

(2).

Table 2. Concentration of sCD14 and sCD163 in the study group

	Statistical parameters	Control	HBV	HCV
sCD14	Mean±SD	35.04 ±6.47	44.2±7.90	46.8±8.9
	P0	-----	0.00017	0.0000
	P1	-----		0.45
	P2 value		<0.00001	
sCD163	Mean±SD	93.009 ±5.94	106.8±9.44	104.32±3.35
	P0		< 0.0000	< 0.0000
	P1			0.38
	P2		< 0.00001	

P0: p value for comparing between control group and each other group, P1: p value for comparing between HBV and HCV, P2: p value for comparing between three groups

ROC analysis was performed using the serum levels of each sCD14 and sCD163 in patients with (HBV and HCV) and a healthy control group according to the presence of the disease. The results of sCD14 in the HBV group were that the area under the curve was 0.83, while in the HCV group, it was 0.86 with P= 0.000. The cut-off for HBV was >38.35, while for HCV was >40.7 and showed a sensitivity of HBV 0.76 and HCV 0.79 while specificity is 0.85 and 0.85, respectively, and the confidence interval CI (CI: 0.71 to 0.94.6) and (CI: 0.75 to 0.96.5) respectively. The results of sCD163 in the HBV group were that the area under the curve was 0.96, while in the HCV group, it was 0.97 with P= 0.000. The cut-off for HBV was >100.12, while for HCV was >100.73 and showed a sensitivity of HBV 0.97 and HCV 0.97 while specificity is 0.85 and 0.90, respectively, and the confidence interval CI (CI: 0.90 to 1.000) and (CI: 0.92 to 1.000) respectively as described in the table (3).

Table 3. ROC curve analysis of sCD14 and sCD163 in the study groups.

		sCD14(HBV)	sCD14(HCV)	sCD163(HBV)	sCD163(HCV)
Area		0.828	0.857	0.957	0.970
Std. Error ^a		0.060	0.055	0.028	0.024
Asymptotic Sig. ^b		0.000	0.000	0.000	0.000
Asymptotic					
95%	Lower	0.71	0.75	0.90	0.92
Confidence	Bound				
Interval					
	Upper	0.95	0.965	1.000	1.000
	Bound				
cut of value		38.35	40.7	100.12	100.73
Specificity		0.85	0.85	0.85	0.90
Sensitivity		0.76	0.79	0.97	0.97

Figure (1) ROC curve analysis for the ability of serum sCD14 to discriminate between patients with HBV and HCV infection and healthy subjects (AUC for HBV = 0.828 and HCV = 0.857).

Figure (2) ROC curve analysis for the ability of serum sCD163 to discriminate between patients with HBV and HCV infection and healthy subjects (AUC for HBV = 0.957 and HCV = 0.970).

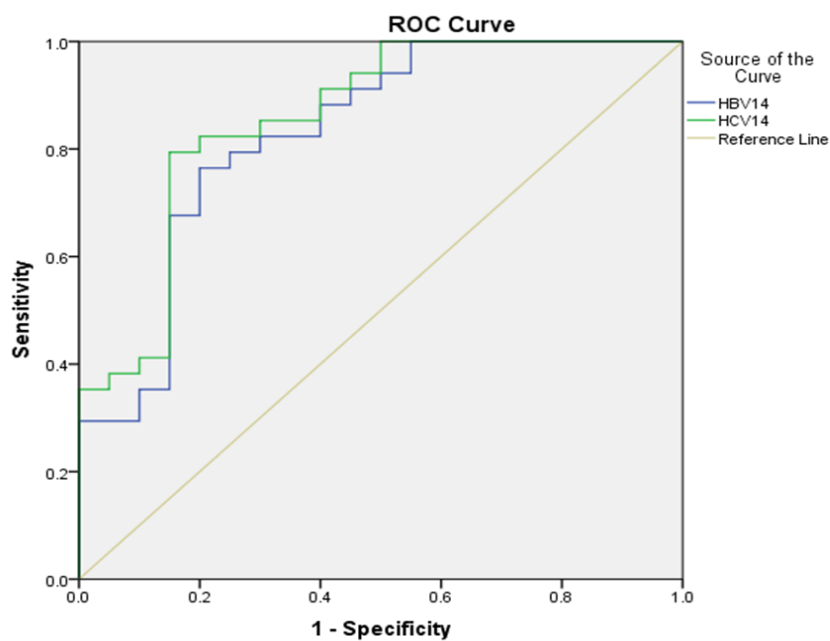


Figure 1. ROC analysis of sCD14 concentrations in the context of discrimination between patients and controls

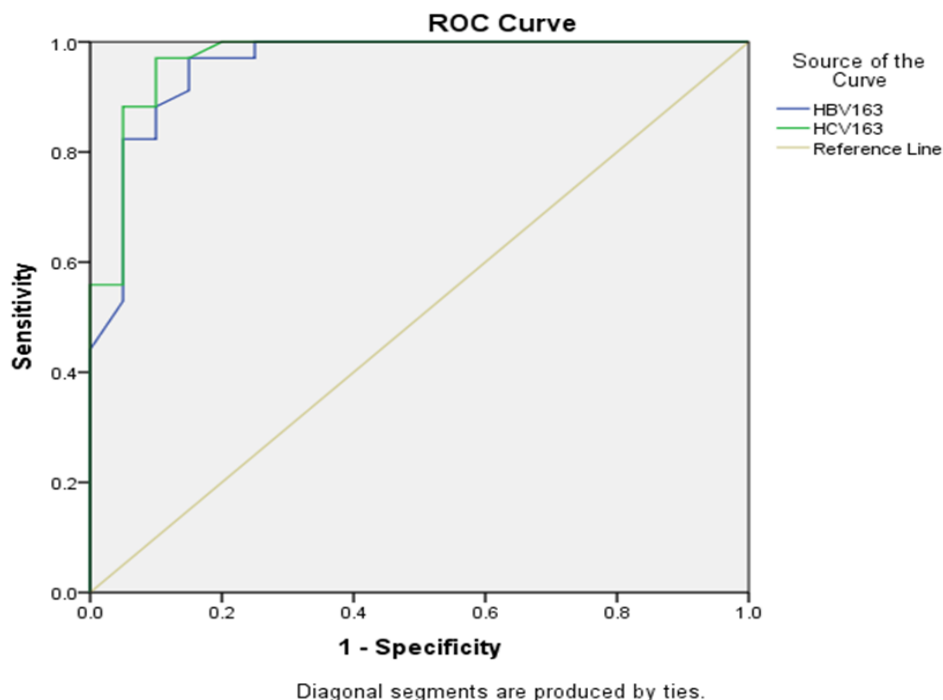


Figure 2. ROC analysis of sCD163 in the context of discrimination between patients and controls

DISCUSSION

The immune response to hepatic viral infection involves innate and adaptive immune mechanisms primarily mediated by Kupffer cells in the liver, and the soluble immune markers sCD14 and sCD163 play a crucial role in this inflammatory response^{16, 17}. This study showed an increase in these two biomarkers (sCD14 & sCD163) in patient groups due to the activation of monocytes and macrophages in response to viral infection, which agrees with previous studies such as^{16, 17, 18, 19, 20}. Many studies have indicated these factors have a vital role in innate immunity which releases into the bloodstream, indicating increased macrophage activation and liver inflammation, and it plays a crucial role in the clearance of haemoglobin-haptoglobin complexes and regulation of the immune response, while in the adaptive response, these cells also capture these viruses, treat them, and present the viral antigens for both viruses to the T cells, which leads to the initiation of this type of response through the production of signal molecules (cytokines), which have a beneficial or harmful role for the host depending on the environmental conditions of this response^{21, 13, 14, 22, 23, 24, 15}, so it can be considered, from my point of view and other research, such as Vercelli and his colleagues in 2001, as one of the links between innate immunity and adaptive immunity because these cells that produce it (monocyte and macrophage) are present

in both types of immunity, which work to present the antigen to the immune system in both kinds of immunity. It has been found in many studies of different viruses that there is a significant increase in these parameters, such as measles, COVID-19, HIV, etc.^{13, 14, 15}. The performance of soluble immune markers sCD14 and sCD163 in differentiating hepatitis B virus (HBV) and hepatitis C virus (HCV) infections was evaluated using receiver operating characteristic (ROC) curve analysis. ROC analysis is a widely used technique in diagnostic testing and biomarker evaluation, through its graphical representation of the true positive rate (sensitivity) plotted against the false positive rate (1 - specificity) for a binary classifier system as the decision threshold will be varied. The area under the ROC curve (AUC) summarises the overall discriminatory power of the test. An AUC of 1.0 indicates perfect discrimination, while an AUC of 0.5 suggests the test is no better than random chance, additionally allowing the identification of the optimal threshold based on the desired balance between sensitivity and specificity. The reasonably wide confidence intervals for sensitivity and specificity indicate the results are statistically significant and less likely to be due to chance. The ROC curve of sCD163 showed better AUC values than sCD14 in HBV and HCV, indicating strong potential to distinguish between patients and healthy individuals. This biomarker demonstrated high sensitivity and acceptable specificity, suggesting accurate identification of individuals with each infection while minimizing false positives. The narrow confidence intervals reported for the performance metrics indicate the results are precise and reliable. Overall, the findings highlight the potential utility of sCD14 and sCD163 as diagnostic biomarkers for HBV and HCV, while emphasizing the need for tailored cut-off values and consideration of the disease stage to optimize the performance of these immune markers. In summary, the ROC analysis highlights the potential utility of sCD14 and sCD163 as diagnostic biomarkers for differentiating HBV and HCV infections from healthy controls. The strong AUC values, high sensitivity and specificity, and reliable statistical significance indicate that these immune markers hold promise as non-invasive tools for the diagnosis and management of viral hepatitis. However, the need for tailored cut-off values based on the underlying viral etiology should be considered to optimize the performance and clinical applicability of these biomarkers.

CONCLUSIONS

In brief, sCD14 is associated with the initiation and perpetuation of inflammation in both HBV and HCV infections, while sCD163 is associated with the resolution and suppression of inflammation. Thus, these biomarkers provide insights into the immune response and inflammatory processes that occur during viral hepatitis, and measuring them in patients' sera can be useful in the monitoring of these diseases. From this nested case-control study, it was found that sCD163 is the most useful biomarker for predicting these two types of viral infection.

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