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The Role of CD8+ T Cells-Producing Interleukin 17 in Pathogenesis of Chronic Hepatitis B

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Abstract

Chronic hepatitis B (CHB) remains a major global public health burden, with approximately 1.1 million deaths annually. The current classification of chronic hepatitis B virus (HBV) infection into four distinct phases is based exclusively on virological, biochemical, and histological parameters without taking into account immunological markers, even though the clinical course and outcome of the infection are mainly linked to the immune response. This study was designed to assess $CD8^{+}IFN\gamma^{+}$ (Tc1), $CD8^{+}IL17A^{+}$ (Tc17) and the expression of perforin and Granzyme B in peripheral blood $CD8^{+}$ T cells to elucidate their functional implications at different phases of chronic hepatitis B infection. Whole blood from 20 chronic Hepatitis B patients and 20 healthy controls recruited respectively at the hepato-gastro-enterology department, CHU Campus and National Blood Transfusion Center (CNTS) of Lomé were stimulated using phorbol 12-myristate 13-acetate (PMA) and ionomycin. $CD8^{+}$, $CD8^{+}IFN\gamma^{+}$, $CD8^{+}IL17A^{+}$, $CD8^{+}Perforin^{+}$ and $CD8^{+}GranzymeB^{+}$ T cells frequency were characterized by intracellular cytokine staining (ICS) combined with flow cytometry method. All patients were positive for anti-HBe and negative for HBeAg. Among them, 7 showed viral replication (active carrier) and 4 showed diseases. We observed that CHB patients displayed a decrease in circulating $CD8^+$ T cells and an increase in $CD8^+IL17A^+$ T cells. This increase in $CD8^+IL17A^+$ T cells was associated with CHB. Our study revealed that $CD8^+$ T cells profile was not impaired at different stages of CHB.

Keywords

Hepatitis B Virus, Chronic Hepatitis B, HBeAg Negative, Cytotoxic T Lymphocytes, CD8 T Cells

1. Introduction

Hepatitis B virus (HBV) is a hepatotropic pathogen capable of establishing persistent infection in humans. Despite the availability of effective vaccines and antiviral treatments, HBV infection remains a significant global health concern, with around 3.2% of the population affected worldwide [1]. According to the World Health Organization (WHO, 2022), approximately 254 million people were living with chronic hepatitis B (CHB) worldwide, surpassing the combined rates of HIV, tuberculosis, and malaria [2] [3]. Each year, CHB is responsible for nearly 1.1 million deaths, predominantly due to complications including cirrhosis and hepatocellular carcinoma [2]. In sub-Saharan Africa, including Togo, data on CHB remain limited even though these regions are considered highly endemic. The immune response plays a crucial role in determining both the control and clinical outcome of HBV infection. Among the principal mediators of antiviral immunity are cytotoxic T lymphocytes ($CD8^+$) and T helper lymphocytes ($CD4^+$), which together orchestrate viral clearance. $CD8^+$ T cells employ two major mechanisms to eliminate infected hepatocytes [4]. The non-cytolytic pathway involves the secretion of pro-apoptotic cytokines such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), which suppress viral replication while sparing hepatocytes from direct destruction. Conversely, in the lytic pathway, $CD8^+$ T cells initiate apoptosis through Fas/Fas ligand (Fas-L) interactions or release cytotoxic granules containing perforin and granzymes, leading to target cell lysis. Among the five known granzymes identified in humans (A, B, H, K, and M), Granzyme B (GzmB) is the most prominent and studied [5]. It is constitutively expressed by $CD8^+$ T lymphocytes and plays a central role in mediating cytotoxic activity [5] [6]. Based on their cytokine secretion profiles, effector $CD8^+$ T cells can be classified into at least two major functional subsets: type 1 cytotoxic T cells (Tc1), which produce IFN-γ and exhibit strong cytotoxic capacities, and type 17 cytotoxic T cells (Tc17), which secrete IL-17 [7]. These subsets have been proposed as promising immunological biomarkers for disease prediction, prognosis, and therapeutic targeting [8]. The differentiation of chronic HBV infection into distinct clinical phases is of critical importance for the individualised management of affected patients [9]. Multiple efforts to define these phases have evolved over time, but knowledge gaps of each phase's immunopathogenesis have led to inconsistent clinical observation-based [10]-[14]. The most recent nomenclature distinguishes between chronic infection and chronic hepatitis, in conjunction with hepatitis B e-antigen (HBeAg) status [11]. However, no immunological marker was taken into account in this classification, despite strong evidence that hepatic injury during HBV infection is largely immune-mediated, primarily driven by cytotoxic T lymphocytes (CTLs) targeting viral antigens [15]. To date, few investigations have explored the heterogeneity of $CD8^+$ T-cell subsets across the various stages of chronic HBV infection. No studies have been conducted in Togo regarding the immunological profile of CHB. The present study was therefore designed to assess the cytotoxic profile of $CD8^+$ T lymphocytes throughout the course of chronic hepatitis B. Specifically, this work examined the expression of interleukin-17A (Tc17), IFN-γ (Tc1), perforin, and Granzyme B in peripheral blood $CD8^+$ T cells to elucidate their functional implications across different phases of chronic hepatitis B infection.

2. Materials and Methods

2.1. Study Population Sample Collection

This study included 20 Togolese patients diagnosed with chronic hepatitis B who were followed at the Hepato-gastro-enterology department, CHU Campus of Lomé and 20 healthy controls (HC) recruited at the National Blood Transfusion Center (CNTS) of Lomé from January to December 2025. Patients with chronic hepatitis B were defined by the following criteria: positive serum hepatitis B surface antigen (HBsAg) at least 6 months before obtaining blood samples [16] or positive serum HBsAg and anti-HBc IgG, anti-HBc IgM negative on one occasion [17]. None of the patients had received antiviral treatment or immunosuppressive therapy before sampling. A semi-structured questionnaire was used to obtain participants' data including demographic and socioeconomic parameters, screening associated signs and symptoms, risk factors and treatment received. Ten mL venous blood samples were collected from each participant in an ethylene diamine tetraacetic acid (EDTA) tube and a tube without an additive.

2.1.1. Exclusion Criteria

For both groups, pregnant women, smokers, patients co-infected with other viruses (hepatitis C virus, hepatitis D virus, human immunodeficient virus), patients with autoimmune liver disease and liver cirrhosis, patients who had received antiviral therapy and patients complicated with other major organ diseases such as cardiovascular and renal diseases were excluded. For healthy controls, those who had abnormal total blood count, elevated liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were also excluded.

2.1.2. Definitions of Chronic HBV Infection Phases among HBeAg Negative Patients

Patients were classified into HBeAg negative chronic infection (HBeAg-infection) phase and HBeAg negative chronic hepatitis (HBeAg-disease) phase [11] [14] [18] after clinical investigations. HBeAg-infection phase is characterized by low (<2000 UI/mL) HBV DNA levels or 2000 UI/mL ≤ HBV DNA < 20,000 UI/mL with persistently normal alanine aminotransferase (ALT). However, HBeAg-disease phase is associated with HBV DNA > 2000 UI/mL and elevated ALT and/or other liver enzyme levels and/or clinical symptoms. According to viral load, they were also divided into active carrier or active replication group, defined as having HBV DNA > 2000 UI/mL and any ALT levels. Inactive carrier group is characterized by HBV DNA < 2000 UI/mL with ALT around the upper limit of normal (ULN), approximately 40 IU/L.

2.2. Ethics Statement

This study was approved by the bioethics committee for health research of Togo ("Comité de Bioéthique pour la Recherche en Santé", CBRS) N˚ 039/2024/CBRS and all participants provided written informed consent before taking part in the study.

2.3. Clinical Indicators Investigation and HBV DNA Detection

The biochemical indicators of liver enzymes, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) were tested in serum samples using an automatic biochemical analyzer cobas c311 (Roche Diagnostics GmbH). The reference values described by Ribeiro *et al.* were used for parameter interpretations [19]. HBV serological markers as antibody to HBcAg (anti-HBc), HBeAg, and antibody to HBeAg (anti-HBe), and alfa-fetoprotein, were detected by the electrochemiluminescence assay (ECLIA) via the Cobas e411 platform (Elecsys; e411 Cobas; Roche Diagnostics Gmb). The white blood cells (WBC) and lymphocyte (LYM) counts were detected by an automatic five-classification blood cell analyzer (Maindray BC-6800, Shenzhen Mindray, China). Viral DNA was extracted according to GXT NA Extraction kit procedures on the automated instrument GenoXtract® (Hain Lifescience, Nerhen, Germany) for plasma samples. To detect and quantify HBV DNA, quantitative real-time polymerase chain reaction (qPCR) was performed with GENERIC HBV CHARGE VIRALE (GHBV-CV) kit (BIOCENTRIC, Bandol, France) using FluoroCycler®XT (Hain Lifescience, Nerhen, Germany) according to the manufacturer's instructions.

2.4. Functional Analysis of $CD8^+$ T Cells

2.4.1. Whole Blood Stimulation

Whole blood (WB) was stimulated in duplicate using 96-wells U-bottom plates (Greiner Bio One, Frickenhausen, Germany) as has been shown before [20]. In brief, 100 µL per well of WB sample were mixed with equal volume of 1X cell stimulation cocktail (PMA, Ionomycin, of Brefeldin A and Monensin) (eBioscience) and RPMI-1640 medium. Then plates were incubated at 37˚C in presence of 5% CO_2 for 6 hours after which red blood cells were lysed from using RBC Lysis Buffer (Roche® Diagnostics GmbH, Mannheim, Germany) according to the manufacturer's instructions.

2.4.2. Panel Configuration

Two separate panels were devised for acquisition to assess $CD8^+$ T-cells functionality. The following fluorochrome-conjugated monoclonal antibodies were used: Panel 1: (CD8-APC, IFNγ-FITC, perforin-PE); Panel 2: (CD8-APC, IL17A-FITC, granzymeB-PE).

2.4.3. Cellular Immunostaining and Phenotyping

After red blood cells lysis, cell-surface staining was performed using CD8-APC (clone SK1) and incubated at 4˚C for 30 mins. Subsequently, cells were washed and permeabilized using Fix-Perm reagent (Invitrogen/Thermo Fisher Scientific) and Fc Receptor (FCR) blocking solution (human TruStainFcX®, BioLegend, San diego, CA, USA) was used according to the manufacturer's instructions to reduce unspecific antibody biding. For intracellular staining, cells were incubated at 4˚C with panel 1) Anti-human IFNγ-FITC (clone 4S.B3) and perforin-PE (clone dG9); panel 2) Anti-human IL17A-FITC (clone BL168) and granzymeB-PE (REF GRB04. After 30 minutes at 4˚C, cells were washed and resuspended in fix-perm buffer for acquisition. In order to test what portion of the cells were dead, although a whole blood sample was used without pretreatment and without additives that could impact cell viability, Zombie Aqua™ Fixable Viability Kit (BioLegend) was included. Data were acquired and analyzed using a flow cytometer (Cytoflex, Beckman Coulter, Brea, California, USA) with CytExpert 2.1 software (Cytoflex, Beckman Coulter, Brea, California, USA). Instruments were calibrated using VersaComp Antibody Capture Bead Kit (Beckman Coulter, CA, USA) and CytoFLEX Daily QC Fluorospheres (Beckman Coulter, CA, USA), respectively, for compensation controls and for daily verification of the flow cytometry optical alignment and fluidics system. Fluorescence Minus One (FMO) controls were customized for each panel, including overlapping markers and unstained cells served as a negative control. The flow cytometry gating strategies are shown in **Figure 1**.

First of all, we searched a quality of run gate based on the time and the SSC-A surface area (**A**), then lymphocytes gate (total T cells) (**B**) were set based on cells granularity and size defined respectively by side scatter (SSC) and Forward scatter (FSC). From them, we evaluated dead and living cells proportions (**C**) before identified $CD8^+$ T-cells (**D**) which were then separated into $CD8^+IL\text{-}17A^+$ (**E**); $CD8^+IFN\gamma^+$ (**F**); $CD8^+Perforin^+$ (**G**) and $CD8^+Granzyme\ B^+$ (**H**).

2.5. Statistical Methods

Data were collected using Excel and statistical analyses were performed with GraphPad Prism version 8.0 (GraphPad Software, San Diego California, USA) and SPSS version 25.0 manufactured by International Business Management (IBM SPSS Statistics version 25; Armonk, NY). The normality of data distribution was assessed by the Kolmogorov-Smirnov test. As the data sets were non-parametric, differences between the two groups were evaluated with non-parametric Mann-

Whitney U tests. Correlation analysis was carried out by Spearman's rank sum correlation. The association between the frequency of total CD8⁺ T cells, Tc1, Tc17 cells, as well as granule expressions with HBeAg negative disease and HBV replication prognosis, was analyzed in binary logistic regressions. Variables with a p-value < 0.20 in the bivariable analyses were subsequently incorporated into the multivariable logistic regression model. Fisher's exact test was used to compare gender frequency. In all analyses, p-value < 0.05 was considered significant.

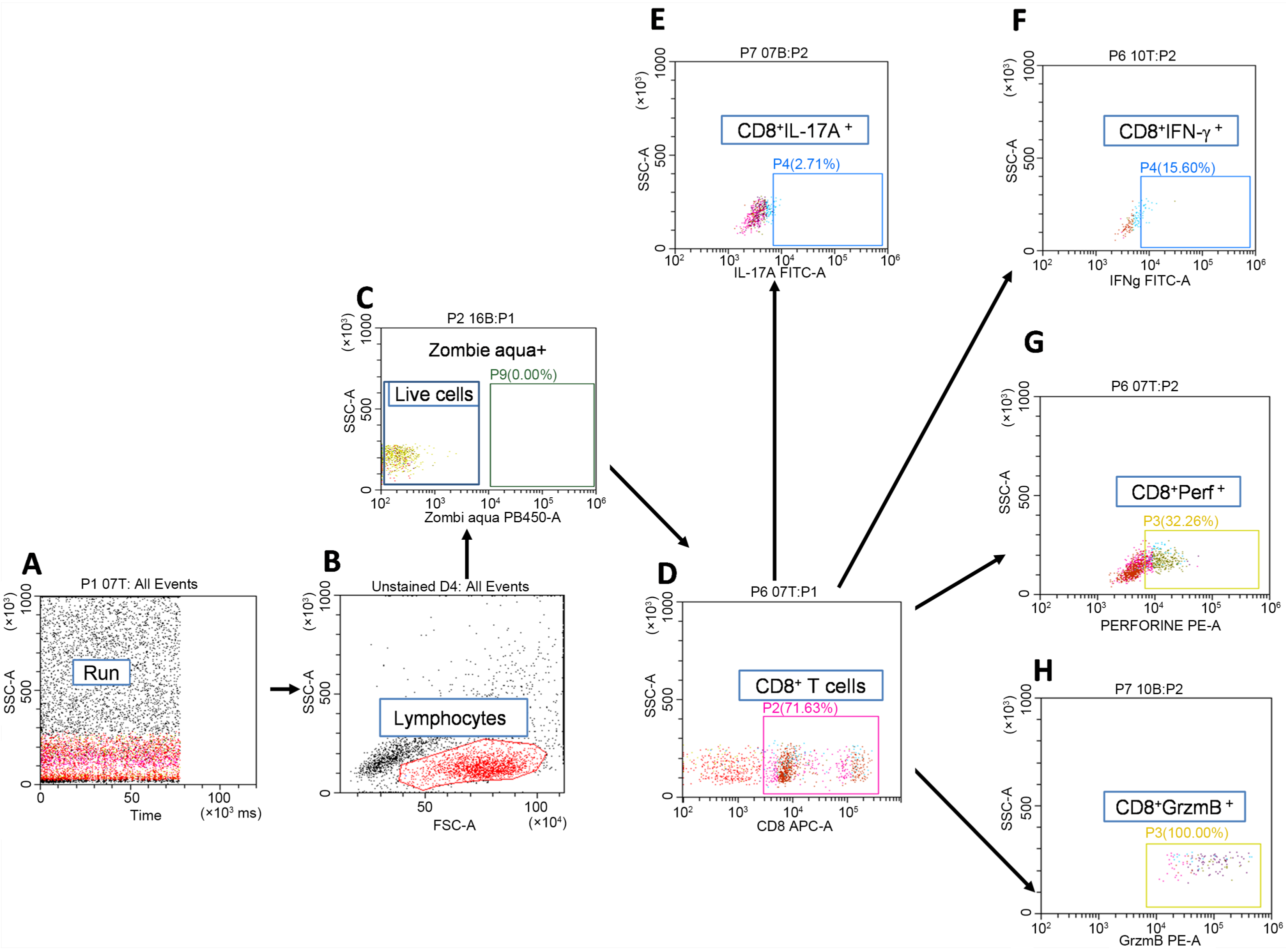


Figure 1. Gating strategies of flow cytometry phenotyping of CD8⁺ T cells.

3. Results

3.1. Study Population Characteristics

We included forty individuals in this study, including 20 chronic Hepatitis B patients (CHB) and 20 healthy controls (HC). Demographic, virological and clinical characteristics of the enrolled subjects were summarized in in Table 1. All patients were positive for anti-HBe, anti-HBc (IgG) and negative for HBeAg, most of them never received a blood transfusion before their infection. The median age of chronic hepatitis B infection patients was 32.50 years and 60% were female, while the healthy controls had a median age of 29.50 years. The patients in HBeAg negative infection phase were the most represented (80%), showing a significant decrease in serum ALT (p = 0.0029), AST (p = 0.0046), and HBV DNA (p = 0.0020) levels compared with those with HBeAg negative hepatitis (20%). Classification of subjects based on viral load showed no statistically significant difference in liver enzyme levels as ALT, AST and others but however, a significant difference was noted in HBV DNA (p = 0.0002) levels (Table 2).

Table 1. Demographic, virological and clinical characteristics of the study population.

Characteristics	Chronic hepatitis B (CHB) (N = 20)	Healthy controls (HC) (N = 20)
Gender		
Male/Female	8/12	19/1
Age (years)		
Median (range)	32.50 (20 - 55)	29.5 (20 - 56)
History of transfusion		
No	19	NA
Yes	1	
ALT (IU/L)		
Median (Range)	23 (6 - 83)	21.5 (12 - 38)
AST (IU/L)		
Median (Range)	27.50 (20 - 65)	NA
AFP (IU/mL)		
Median	2.29	NA
(Range)	(0.79 - 205.50)	
GGT (IU/L)		
Median (Range)	32 (16 - 189)	NA
ALP (IU/L)		
Median (Range)	65 (5 - 816)	NA
HBV DNA (IU/mL)		
Median	291.50	NA
(Range)	(18 - 433,000)	
Anti-HBe (+ve)		
Number	20	NA
Percentage (%)	100	
HBeAg (−ve)		
Number	20	NA
Percentage (%)	100	
Anti-HBc (+ve)		
Number	20	NA
Percentage (%)	100	
Total of WBC/mm³		
Median	4690	4785
(Range)	(3180 - 8640)	(3530 - 6030)

Continued

Total lymphocytes/mm³		
Median	1830	2040
(Range)	(350 - 3520)	(1500 - 3120)

NA: not applicable, ALT: alanine aminotransferase; Reference values in chronic hepatitis: <31 U/L (women) and 37 U/L (men); AST: aspartate aminotransferase; Reference values in chronic hepatitis: <31 U/L (women) and <41 U/L (men); GGT: gamma-glutamyl transferase; Reference values 8 - 61 U/L (men) and 5 - 36 U/L (women); ALP: alkaline phosphatase; Reference values 40 - 150 U/L; AFP: alfa-fetoprotein; Reference values ≤ 5 U/L; WBC: white blood cells. HBsAg: hepatitis B surface antigen; HBeAg (−ve): hepatitis B e-antigen negative; Anti-HBc (+ve): hepatitis B core antibody positive; Anti-HBe (+ve): hepatitis B e-antibody positive; HBV DNA: hepatitis B virus desoxyribose nucleic acid.

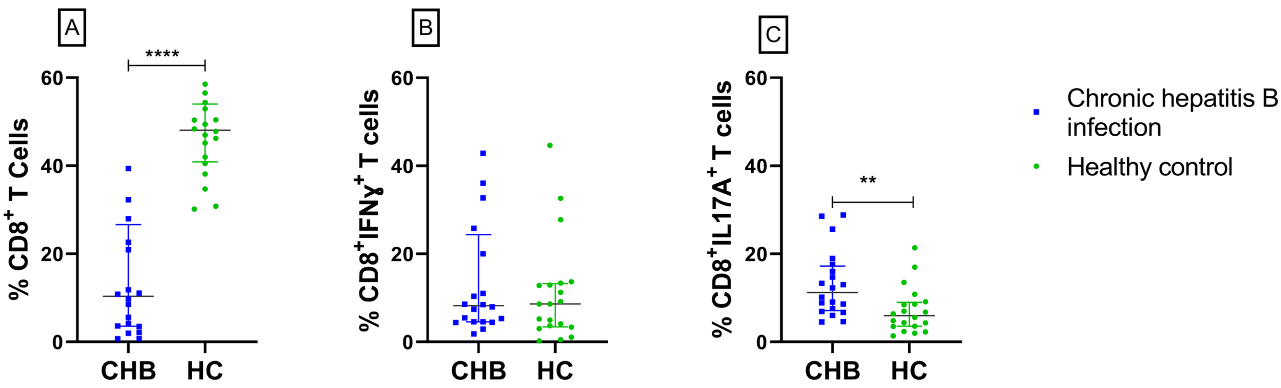
Table 2. Comparison of clinical indexes at different phases of chronic hepatitis B.

Characteristics	HBeAg negative infection (N = 16)	HBeAg negative disease (N = 4)	Inactive carrier (N = 13)	Active carrier (N = 7)	p-value 1 (e-CI Vs e-CHB)	p-value 2 (AC Vs IC)
Gender						
Male/Female	7/9	1/3	5/8	3/4	0.6186	>0.9999
Age (years)						
Median (Range)	32.50 (20 - 55)	29.00 (24 - 43)	34 (20 - 55)	29 (24 - 49)	0.3179	0.8426
AST (IU/L)						
Median (Range)	24 (20 - 44)	46 (33 - 65)	24 (20 - 50)	33 (20 - 65)	**0.0029**	0.1688
ALT (IU/L)						
Median (Range)	19.50 (6 - 50)	44.50 (34 - 83)	20 (6 - 44)	34 (8 - 83)	**0.0046**	0.1913
AFP (IU/mL)						
Median	2.29	2.23	2.23	2.34	0.2578	0.7513
(Range)	(0.79 - 13.10)	(1.24 - 205.50)	(0.79 - 13.10)	(1.13 - 205.50)		
GGT (IU/L)						
Median (Range)	32 (16 - 70)	63 (25 - 189)	33 (16 - 70)	26 (20 - 189)	0.1008	0.2024
ALP (IU/L)						
Median (Range)	65 (4 - 109)	67 (55 - 816)	67 (4 - 109)	62 (50 - 816)	0.4066	0.4370
HBV DNA (IU/mL)						
Median	136.50	27,450	91	11,800	**0.0020**	**0.0002**
(Range)	(18 - 11800)	(8300 - 433,000)	(18 - 1220)	(3620 - 433,000)		
Total of WBC/mm³						
Median	4690	4895	4640	5340	0.4812	0.4812
(Range)	(3680 - 8180)	(3180 - 8640)	(3680 - 6170)	(3180 - 8640)		
Lymphocytes/mm³						
Median	1875	1435	1900	1590	0.1386	0.2346
(Range)	(1270 - 2970)	(350 - 3520)	(1270 - 2970)	(350 - 3520)		

NA: not applicable, ALT: alanine aminotransferase; Reference values in chronic hepatitis: <31 U/L (women) and 37 U/L (men); AST: aspartate aminotransferase; Reference values in chronic hepatitis: <31 U/L (women) and <41 U/L (men); GGT: gamma-glutamyl transferase; Reference values 8 - 61 U/L (men) and 5 - 36 U/L (women); ALP: alkaline phosphatase; Reference values 40 - 150 U/L; AFP: alfa-fetoprotein; Reference values ≤ 5 U/L; WBC: white blood cells; e-CI: HBeAg negative infection; e-CHB: HBeAg negative disease; AC: Active carrier; IC: Inactive carrier.

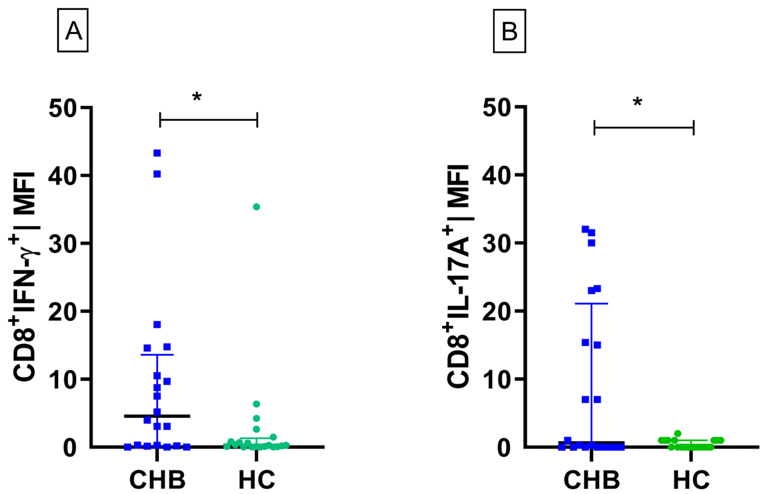
3.2. Increased CD8⁺IL17A⁺ T Cells (Tc17) in Patients with Chronic HBV Infection

Cytotoxic T lymphocytes ($CD8^+$ T cells) and their subsets were characterized in blood from both healthy control and chronic hepatitis B infection groups. We observed that compared to the healthy control group, the total percentage of $CD8^+$ T cells was significantly decreased ($p < 0.0001$) in chronically infected subjects (**Figure 2(A)**). We also found that CHB subjects exhibited higher frequencies of $CD8^+$ T lymphocytes that expressed IFNγ(Tc1) (**Figure 2(B)**) and IL-17A (Tc17), although this was only significant for $CD8^+IL17A^+$ T cells ($p = 0.0029$) (**Figure 2(C)**). Interestingly, both the $CD8^+IFN\text{-}\gamma^+$ ($p = 0.0153$) and $CD8^+IL17A^+$ ($p = 0.0227$) mean fluorescence intensity (MFI) were higher in this subject (**Figure 3**).



Data are expressed as median with interquartile range. Each dot represents an individual data point, and the horizontal black lines represent the median. CHB: chronic hepatitis B group (N = 20); HC: healthy control group (N = 20); The number of asterisks in the figures indicates the level of statistical significance (****$p < 0.0001$; **$p < 0.01$).

Figure 2. The percentage of circulating $CD8^+$ T cells and their subsets in CHB patients and healthy controls.

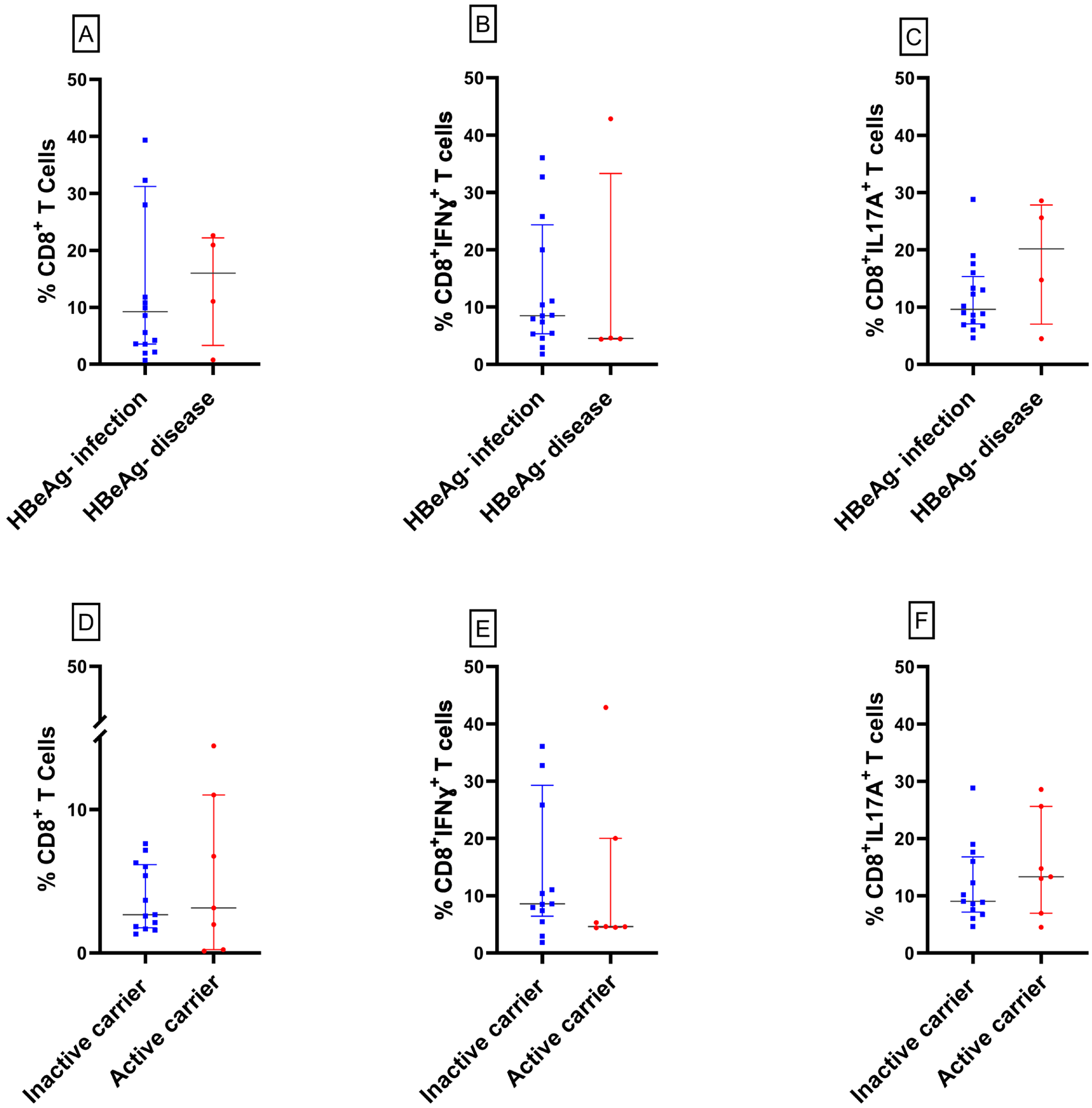


Data are expressed as median with interquartile range of the mean fluorescence intensity of IFN-γ(A) and IL-17A (B). CHB: chronic hepatitis B group (N = 20); HC: healthy control group (N = 20); (*$p < 0.05$).

Figure 3. Comparison of $CD8^+IFN\text{-}\gamma^+$ and $CD8^+IL17A^+$ T cells mean fluorescence intensity (MFI) between CHB and HC.

3.3. Viral Replication Did Not Influence the $CD8^+IL17A^+$ T Cells Population

The evaluation of $CD8^+$ T cells and their subsets was carried out at different stages of chronic hepatitis and according to viral activity. No significant difference was found in $CD8^+$ T cells percentage at different stages, whether in HBeAg negative phases (Figure 4(A)) or in the viral load phases (Figure 4(D)), nor in the percentage of $CD8^+IFN\gamma^+$ T cells (Figure 4(B) and Figure 4(E)) and even $CD8^+IL17A^+$ T cells (Figure 4(C) and Figure 4(F)).

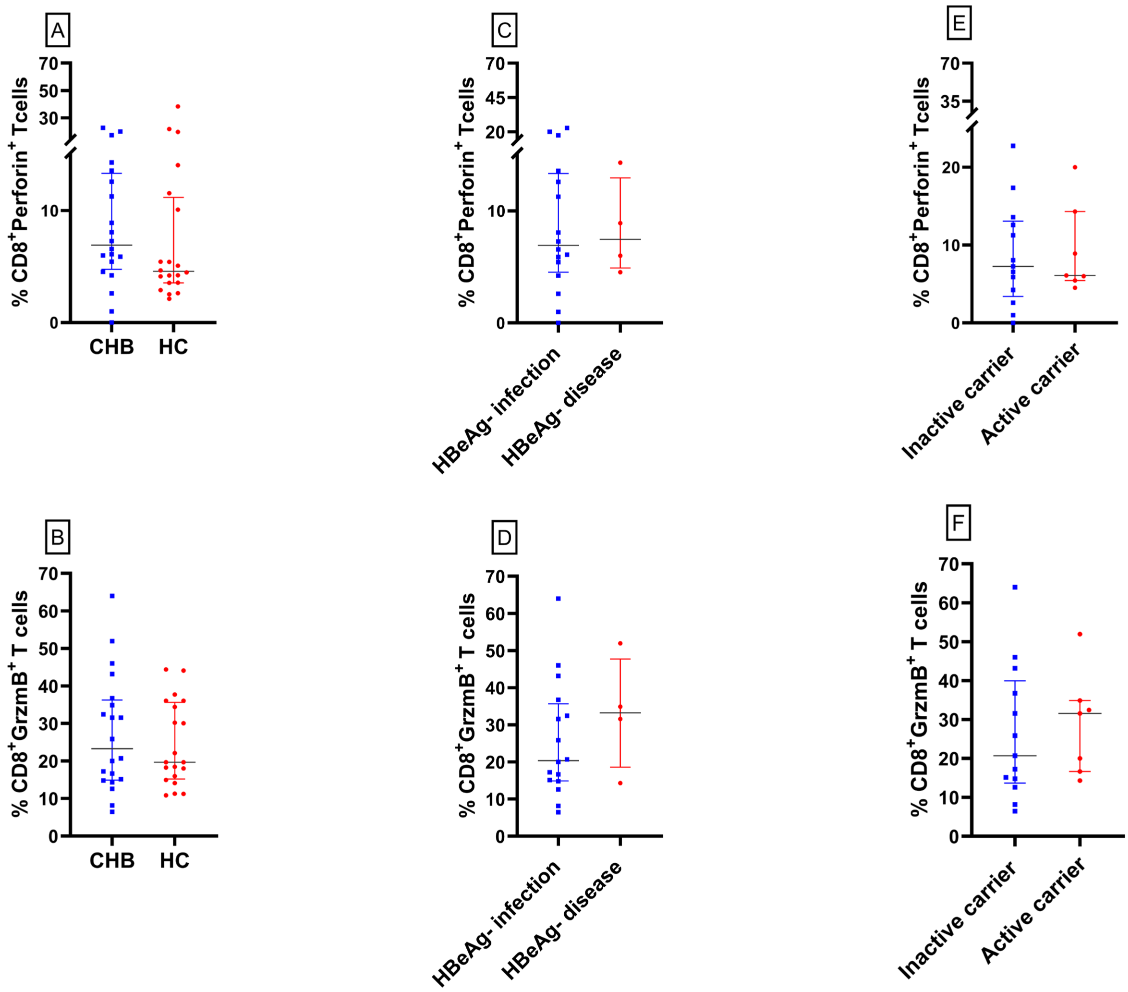


Data are expressed as median with interquartile range. Each dot represents an individual data point, and the horizontal black lines represent the median. Comparison of $CD8^+$ T cells according to HBeAg negative phases (A) and viral load phases (B); Comparison of $CD8^+$ T producing IFNγ(Tc1) at different stages of chronic hepatitis B infection according to HBeAg negative (C) and viral load (D); Comparison of $CD8^+IL\text{-}17A^+$ T cells at different stages of chronic hepatitis B infection according to HBeAg negative (E) and according to viral load (F). HBeAg-infection (N = 16); HBeAg-disease (N = 4); inactive carrier (N = 13); active carrier (N = 7).

Figure 4. Comparison of $CD8^+$ T cells and it subsets percentage at different stages of chronic hepatitis B.

3.4. Unimpaired Cytotoxic Function of Circulating CD8+ T Cells in Patients with Chronic Hepatitis B

Considering that CD8+ T cells functionality is associated with progression to chronic hepatitis B, we then focused our analyses on their local function corresponding to the expression of cytotoxic molecules as perforin and granzyme B in the blood. The results showed that the frequencies of CD8+Perforin+ (**Figure 5(A)**) and CD8+GzmB+ (**Figure 5(B)**) T cells were not altered among CHB group compared to healthy controls. Similarly, no difference in Perforin (**Figure 5(C)**) and granzyme B (**Figure 5(D)**) expression by CD8+ T cells at HBeAg negative phases as well as at different stages according to viral load (**Figure 5(E)** and **Figure 5(F)**).



Comparison of CD8+perforin+ T cells **(A)** and CD8+granzymeB+ T cells **(B)** between chronic hepatitis B infection (CHB) group (N = 20) and HC, healthy control (N = 20). Perforin [**(C)**, **(E)**] and Granzyme B [**(D)**, **(F)**] expression by CD8+ T cells was also compared at different phases of chronic hepatitis B. The data are expressed as median with interquartile range. Each dot represents an individual data point, and the horizontal black lines represent the median. Statistical analysis was performed using a Mann-Whitney test. HBeAg-infection (N = 16); HBeAg-disease (N = 4); inactive carrier (N = 13); active carrier (N = 7).

Figure 5. Cytotoxic function of circulating CD8+ T cells from chronic hepatitis B patients.

3.5. Alkaline Phosphatase Serum Level Is Negatively Correlated with $CD8^+$ T Cells Frequency

The correlation of six clinical indexes, namely HBV DNA, ALT, AST, GGT, AFP, ALP levels on one hand and the expression of perforin and granzyme B by $CD8^+$ lymphocytes on the other hand, with total $CD8^+$ T cells, $CD8^+IFN\gamma^+$ and $CD8^+IL17A^+$ frequency was analyzed using the Spearman rank test. Alkaline phosphatase (ALP) serum level was negatively correlated with $CD8^+$ T cells frequency (r = −0.678, p = 0.0010) in HBeAg negative CHB. In contrast, all five clinical parameters showed no correlation with $CD8^+$ T cell subset frequencies (Table 3). A positive correlation was observed regarding perforin (r = 0.582, p = 0.007) expression with $CD8^+IFN\gamma^+$ and $CD8^+IL17A^+$ frequency.

Table 3. Correlation of ALT, DNA HVB, ALP and GGT serum levels, % $CD8^+Perf^+$ and % $CD8^+GrzmB^+$ with $CD8^+$ T cells subsets frequencies in patients with CHB.

	% $CD8^+$ T cells		% $CD8^+IFN\gamma^+$ (Tc1)		% $CD8^+IL17^+$ (Tc17)	
	Rho (rs)	p-value	Rho (rs)	p-value	Rho (rs)	p-value
HBV DNA (IU/mL)	0.082	0.731	−0.187	0.431	0.380	0.089
ALT (IU/L)	0.018	0.940	−0.250	0.288	0.004	0.987
AST (IU/L)	−0.010	0.967	−0.290	0.214	−0.004	0.987
AFP (IU/mL)	0.159	0.502	0.185	0.435	0.417	0.068
GGT (IU/L)	−0.318	0.172	0.250	0.288	0.146	0.0539
ALP (IU/L)	**−0.678**	**0.001**	0.111	0.640	−0.018	0.940
% $CD8^+Perf^+$	0.006	0.980	**0.582**	**0.007**	**0.535**	**0.015**
% $CD8^+GrzmB^+$	0.026	0.915	−0.122	0.416	0.251	0.286

ALT, alanine aminotransferase; HBV DNA, hepatitis B virus desoxyribose nucleic acid; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase. Spearman's correlation rank test was used for analyses.

3.6. The Elevated $CD8^+IL17A^+$ T Cells (Tc17) Frequency Are Associated with Chronic HBV Infection

Binary logistic regression analysis was performed to search for possible association between immunological parameters (total $CD8^+$ T cells and their subpopulations) and Chronic Hepatitis B. Univariate analysis indicated a significant association between total $CD8^+$ T cells (p = 0.001, odd ratio (OR) = 0.909; 80% confidence interval (CI) = 0.877 - 0.942), Tc17 (p = 0.017, OR = 1.176; 80% CI = 1.078 - 1.282), and CHB infection (Table 4). In multivariate analysis, total $CD8^+$ T cells (aOR = 0.879, p = 0.002; 95% CI = 0.811 - 0.953) and Tc17 (aOR = 1.302, p = 0.008; 95% CI = 1.072 - 1.582) remained significantly associated with CHB. Among the 20 CHB patients included in our study, 7 showed viral replication (active carrier) and 4 showed symptoms and or disease (HBeAg negative disease). The correlation between the frequency of total $CD8^+$, $CD8^+IFN\gamma^+$, $CD8^+IL17A^+$ T cells and granules expressions with HBeAg negative disease and viral load prognosis was also analyzed using binary logistic regression (Table 5). The results revealed that only $CD8^+IL17A^+$ T cells frequency was independent risk factor for HBeAg negative disease (p = 0.027, OR = 1.207, 80% CI = 1.022 - 1.427) and for HVB replication (p = 0.028, OR = 1.184, 80% CI = 1.018 - 1.378).

Table 4. Logistic regressions between CHB infection and $CD8^+$ T cells response.

Factors (%)	Univariate		p-value	Multivariate		p-value
	OR	CI (80%)		aOR	CI (95%)	
HBe negative CHB (N = 20) + Healthy control (N = 20)						
$CD8^+$ T cells	**0.909**	**(0.877 - 0.942)**	**0.001**	**0.879**	**(0.811 - 0.953)**	**0.002**
Tc1	1.023	(0.993 - 1.055)	0. 333			
Tc17	**1.176**	**(1.078 - 1.282)**	**0.017**	**1.302**	**(1.072 - 1.582)**	**0.008**
$CD8^+Perf^+$	1.007	(0.954- 1.063)	0.866			
$CD8^+GrzmB^+$	1.017	(0.985 - 1.049)	0.500			

Tc1 = $CD8^+IFN\gamma^+$T cells; Tc17 = $CD8^+IL17A^+$ T cells; OR: odds ratio; CI: confidence interval.

Table 5. Binary logistic regression analysis of HBeAg negative disease and replication risk factors.

Factors (%)	Univariate		p-value
	OR	CI (80%)	
HBeAg negative disease[a] (N = 4) + Healthy control (N = 20)			
$CD8^+$ T cells	0.014	0.000	0.994
$CD8^+IFN\gamma^+$ (Tc1)	1.018	(0.967 - 1.072)	0.661
$CD8^+IL17^+$ (Tc17)	**1.207**	**(1.082 - 1.347)**	**0.027**
$CD8^+Perf^+$	0.999	(0.916 - 1.089)	0.985
$CD8^+GrzmB^+$	1.064	(1.001 - 1.132)	0.196
Active carrier[a] (N = 7) + Healthy control (N = 20)			
$CD8^+$ T cells	0.589	(0.358 - 0.968)	0.172
$CD8^+IFN\gamma^+$ (Tc1)	1.008	(0. 963 - 1.056)	0.814
$CD8^+IL17^+$ (Tc17)	**1.184**	**(1.073 - 1.308)**	**0.028**
$CD8^+Perf^+$	1.012	(0.946 - 1.082)	0.820
$CD8^+GrzmB^+$	1.034	(0.985 - 1.086)	0.379

[a]Dependent variables, Tc1 = $CD8^+IFN\gamma^+$T cells ; Tc17 = $CD8^+IL17A^+$ T cells; OR: odds ratio; CI: confidence interval.

In summary, in patients with chronic hepatitis B, a decrease in circulating $CD8^+$ T lymphocytes and an increase in $CD8^+IL17A^+$ T lymphocytes were observed compared to healthy controls. This elevated $CD8^+IL17A^+$ T lymphocytes was associated with chronic hepatitis B.

4. Discussion

Chronic hepatitis B (CHB) increases morbidity and mortality due to the risk of the development of liver cirrhosis and hepatocellular carcinoma [2]. Recent nomenclature of the four phases of CHB is based only on virological and biochemical parameters, while the outcome of the infection is mainly linked to the host's immune response [11] [12] [14]. Host responses reflected by immune markers are not considered in this definition [9]. $CD8^+$ T cells and their subsets play a crucial role in virus clearance and are suggested to have significant potential as biomarkers for disease prediction and prognosis [8]. In this study, we investigate the cytotoxic state of $CD8^+$ T cells and their subsets during CHB. HBeAg negative chronic HBV infection represents the majority of the total chronic hepatitis B patient population in many areas and varies from 52.5% to 100% [21]-[25]. In our study, HBeAg negativity was found at 100% [26]. This variation in this prevalence has been linked to the distribution of HBV genotypes in addition to differences in the age of infected subjects as reported by several authors [27] [28]. HBeAg negative chronic HBV infection can be divided into two phases according to ALT values, viral load (DNA HBV) levels and eventually the presence or absence of liver inflammation [11] as HBeAg negative infection and HBeAg negative disease. ALT ($p = 0.0046$) and AST ($p = 0.0029$) serum levels were significantly increased in HBeAg negative disease patients in comparison with HBeAg negative infection group, suggestive of liver injury in this group. $CD8^+$ T cells and its main subsets characterization revealed a significant decrease in the percentage of total $CD8^+$ T cells in CHB compared to healthy controls. This aligns with Korobova *et al.* and Xie *et al.*, who reported a depletion of these cells in CHB [29] [30]. The decrease in $CD8^+$ T cells frequency may probably due to the migration of these cells from the peripheral blood to the liver tissue. In addition, HBV lymphotropism towards $CD8^+$ T cells has also been proposed [31]. In contrast, our finding demonstrated a higher percentage of $CD8^+IFN\gamma^+$ (Tc1) and $CD8^+IL17A^+$ (Tc17) T cells in CHB, although this was only significant for $CD8^+IL17A^+$ T cells, suggesting differential response of the two main cellular subsets. Likewise, in a study by Zhang *et al.* [32], Tc17 were significantly increased in CHB patients. Interleukin-17 (IL-17) has been implicated in both protective and pathogenic immune responses (pathologic inflammation) during viral infection [7] [33]. The increase subtype 17 of T cytotoxic lymphocyte cells ($CD8^+IL17A^+$) reflects their important role at this stage of the infection, requiring further investigation. No significant difference in the expression of granzyme B and perforin was observed between patients with chronic hepatitis B and healthy controls. This finding contrasts with previous reports suggesting that during CHB, $CD8^+$ T cells impairment is not only quantitative but also functional [30]. This contradiction may be attributed to the fact that our participants are all at the HBeAg/Anti-HBe seroconversion stage. Thus, this stage is generally associated with immune control [34], implying that $CD8^+$ T cell functionality may have been restored after HBeAg/Anti-HBe seroconversion, thus reflecting a partial reconstitution of the $CD8^+$ T cells dysfunction despite the persistence of HBV. In our study, the analysis of correlations between the most useful clinical and biological parameters (HBV DNA, ALT) and $CD8^+$, $CD8^+IFN\gamma^+$, $CD8^+IL17A^+$, $CD8^+Perforin^+$ and $CD8^+GzmB^+$ T cells did not show any statistically significant associations. This finding is consistent with that of Xie *et al.* [30], whose study focused on the occurrence of acute and chronic hepatitis B. Interestingly our results revealed a negative correlation between alkaline phosphatase

(ALP) serum level ($r = -0.678$, $p = 0.0010$) and $CD8^+$ T cells frequency. This means that if peripheral $CD8^+$ decreases, ALP increases. Clinically, an elevated ALP is often associated with cholestasis, an obstruction of the bile ducts that prevents the flow of bile. Significant decrease in $CD8^+$ T cells frequency could be a contributing factor to cholestasis in CHB. Indeed, the decrease in circulating $CD8^+$ T cells would reflect their migration to the liver to exert their cytotoxic functions against infected hepatocytes. This hepatic cytotoxicity could contribute to hepatocyte destruction (cytolysis) with a risk of cholestasis through disruption of bile formation and excretion. Interleukin-17 was suggested as a potential biomarker in cancer [35] and viral infection [36]. Thereby, we investigated the potential of cytotoxic T cells producing IL-17 ($CD8^+IL17A^+$), IFN-γ ($CD8^+IFN\gamma^+$) in CHB. Total $CD8^+$ T cells ($p = 0.001$, OR = 0.909) and $CD8^+IL17A^+$ ($p = 0.017$, OR = 1.176) are both associated to CHB and respectively constitute a protective and a risk factor. The prognosis model highlights that only $CD8^+IL17A^+$ subpopulations frequency may be determinant for HBeAg negative disease ($p = 0.027$, OR = 1.207) and active carrier ($p = 0.028$, OR = 1.184) prognosis. We recognize some limitations inherent to our study. Firstly, the relatively small sample size constitutes a major limitation leading to reduced statistical power and validity of the prognosis model at different stages as well as the generalizability of the results. Secondly, the analyses were performed only on peripheral blood, without exploring intrahepatic $CD8^+$ T cells and without the cytotoxicity mechanism involving the Fas/Fas-L pathway. This may not adequately represent the events that occur in the liver.

5. Conclusion

The mechanisms underlying the immunopathogenesis involving $CD8^+IL17A^+$ T cells (Tc17) in chronic hepatitis B remain under investigation. This study highlighted that high frequency of $CD8^+IL17A^+$ T cells are associated with chronic hepatitis B. Nevertheless, in light of these findings, further investigations requiring a larger cohort with liver tissue samples are needed to explore their mechanisms of pathogenesis and their usefulness in the immunological biomarkers development of chronic hepatitis B.

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Conflicts of Interest

The authors declare no conflict of interest.

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