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Interleukin 6 rs1800795 Polymorphism, an Emerging Risk Factor in the Progression of HBV in West Africa

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Abstract

Introduction: The course of hepatitis B virus (HBV) infection is primarily influenced by the virus itself, the immune response, and genetic diversity. Numerous studies confirm that host genetic diversity plays a significant role in the progression of HBV infection. Genetic factors such as single nucleotide polymorphisms (SNPs) in various genes are implicated in the variability of the clinical course of HBV infection. Recent studies have shown that cytokine genetic polymorphisms are associated with the development of chronic HBV infection and its progression. The present study examined the association between the IL6 gene polymorphism rs1800795 and other HBV-related diseases and its genetic susceptibility to chronic HBV infection in Togo. **Methodology:** Genotyping of the IL6 gene polymorphism rs1800795 was performed on 146 participants, comprising 92 cases (29 with chronic hepatitis B, 41 with cirrhosis, and 22 with hepatocellular carcinoma) and 54 healthy controls, using PCR-RFLP. The SfaNI enzyme was used for enzymatic digestion. Statistical analysis was performed using SPSS version 20 and Epi Info version 7.5.2.0. **Results:**

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The genotypic frequencies of the IL6 gene polymorphism rs1800795: GG, GC, and CC were 14.13%, 76.09%, and 9.78%, respectively, in cases and 31.49%, 55.55%, and 12.93% in controls. The frequency of the wild-type allele G was 52.17% in cases and 59.26% in controls, with no significant difference ($p > 0.05$). In the general population, it is as follows: 20.55% for the GG genotype, 68.49% for the GC genotype, and 10.96% for the CC genotype; the frequency of the G allele was 54.79% and that of the C allele is 45.21 %. Following this comparison, a major risk factor for the progression of HBV infection to severe forms was statistically significantly associated with the GC genotype of rs1800795 in the subgroup of healthy subjects to liver cirrhosis (OR = 3.02; 95% CI: 1.05 - 8.68; $p = 0.03$) and to hepatocellular carcinoma (OR = 4.81; 95% CI: 0.99 - 23.41; $p = 0.03$). **Conclusion:** Our study is the first investigation conducted in Togo to evaluate the association between the rs1800795 polymorphism of the IL6 gene and the progression of HBV infection. It showed that the heterozygous GC genotype of rs1800795 seems to be a risk factor associated with the progression of HBV to liver cirrhosis and hepatocellular carcinoma.

Keywords

HBV, IL6, Polymorphism, Gene, Togo

1. Introduction

Hepatitis B is a life-threatening liver infection caused by the hepatitis B virus (HBV). It is a major public health problem worldwide [1] [2]. The WHO estimates that approximately 254 million people are living with chronic hepatitis B. It is responsible for about 1.2 million new infections each year [3]-[5] and causes about 250,000 deaths annually worldwide [1]. More than 65 million people have chronic infection in Africa [5] [6]. In sub-Saharan Africa, the prevalence rate of HBV is between 8% and 18%, making it an area of high endemicity [3] [7]. The prevalence of HBV in Togo varies between 13% and 16% [3] [8] [9]. In 2021, Bitty-Anderson *et al.,* a prevalence of 9.9% was estimated in a study in Lomé [10]. Dossim *et al.,* in 2025, found 8.76% in a seroprevalence study of HBV and HIV in Kara [11]. A prevalence of nearly 35% [3] [8] is estimated in the prefectures of the far north, such as Dapaong, a city located in the far north of the country, thus highlighting the hyperendemicity of the infection. HBV infection can lead to numerous clinical complications, such as chronic hepatitis, liver failure, cirrhosis, and hepatocellular carcinoma [1] [2] [11] [12]. In 2022, hepatitis B was responsible for approximately 1.1 million deaths, mainly due to cirrhosis or hepatocellular carcinoma (primary liver cancer) [5].

These complications result not only from the direct cytopathic effect of the virus itself, but also from the host's immune response, which influences disease progression [13] [14]. It is also influenced by genetic diversity [15]-[17]. Genetic fac-

tors such as single nucleotide polymorphisms (SNPs) in various genes are implicated in the variability of the clinical course of HBV infection [18]-[24]. In this context, the analysis of genetic factors appears particularly relevant for identifying prognostic markers and for better understanding the progression of the infection [25]. Studies have revealed that numerous human genes can confer protection or promote the progression of the infection to severe forms of the disease, specifically the *p53* and *RB1* (Retinoblastoma 1) genes [26] [27], the *GSTs* gene, (glutathione S-transferases) [28] [29], the *ECM1* gene (extracellular matrix protein 1) [30] [31], interleukins (IL6 and IL10) [1].

Recent studies have shown that genetic polymorphisms of cytokines participate in the regulation of hepatocyte functions and play a fundamental role in the immunopathogenesis of HBV infection by being associated with the development of chronic infection and its progression to liver tumors [1] [32]. Interleukin 6 (IL6) is a potent, multifunctional, and pleiotropic pro-inflammatory cytokine involved in stimulating the innate immune response [33] [34]. It plays a crucial role in regulating the immune and biological responses of several target cells, including hepatocytes [35] [36]. Kuo *et al.* showed that IL6 was able to efficiently suppress HBV replication and prevent the accumulation of covalently closed circular DNA (cccDNA) of HBV in a human hepatoma cell line [37]. According to numerous studies, IL-6 expression increases differentially in response to inflammation, infection, and the presence of certain tumors [37]-[39]. Another study suggested that IL-6 gene polymorphisms may be associated with the outcome of allogeneic hematopoietic stem cell transplantation, particularly in patients transplanted from a related donor [40]. However, the exact mechanism involving IL-6 in the progression of HBV infection remains unknown. The present study, the first in Togo, aims to examine the association between the IL-6 gene polymorphism rs1800795 and genetic susceptibility in the progression of chronic HBV infection.

2. Methods

2.1. Period, Type, and Study Population

2.1.1. Type and Period of the Study

The study was conducted at Ouagadougou, Burkina Faso. Of the 146 study participants, 92 were cases and 54 were healthy controls. Samples were collected in Togo, specifically at the University Hospital Center Campus de Lomé for the cases and at the Togolese National Blood Transfusion Center (CNTS) for the controls in Lomé. This was an analytical case-control study that evaluated the role of the IL6 gene polymorphism rs1800795 in the progression of HBV infection. The study took place over a period of twenty-six months, including the data collection period (February 2024 to March 2026).

2.1.2. Study Population

The study population consisted of patients with chronic hepatitis B, liver cirrhosis B, hepatocellular carcinoma due to hepatitis B who came for a consultation or treatment at the CHU Campus of Lomé and controls were sampled from blood

donation at the CNTS. It comprised two distinct cohorts: cases and controls. The case cohort consisted of individuals diagnosed with chronic hepatitis B (HCB), hepatitis B viral cirrhosis, and hepatocellular carcinoma attributed to HBV infection. Conversely, the control cohort included individuals who are tested negative for HBsAg, anti-HCV antibodies and HIV.

2.2. Inclusion and Exclusion Criteria

2.2.1. Inclusion Criteria

- **Chronic hepatitis B:** Participants in this group had a confirmed HBV infection for over six months, evidenced by HBsAg positivity, and ultrasound results showing no significant liver abnormalities.
- **Cirrhosis:** Participants in this category had a clinically confirmed cirrhotic liver condition, with HBV being the sole etiological agent.
- **Hepatocellular carcinoma:** Enrollment was based on alpha-fetoprotein (AFP) assay results, computed tomography (CT) scan findings, and/or histological liver examination. Only individuals with HBV as the sole exposure factor were considered.
- **Control group:** Participants who are tested negative for HBsAg, anti-HCV, and HIV during a blood donation. It should be noted that the control samples were collected at the National Blood Transfusion Center (CNTS) in Lomé. These samples came from blood donors, and during the transfusion process, we took the opportunity to collect them in our tubes. After the transfusion, the CNTS immunoserology laboratory analyzed the donors' blood for hepatitis markers and other parameters to eliminate any samples that could compromise the blood transfusion. Only after this analysis was a list of healthy subjects provided to us so that we could eliminate those not meeting our study criteria.

2.2.2. Non-Inclusion Criteria

Exclusions encompassed HBV-negative cases, HCV-positive cases, HDV-positive cases, HIV-positive cases, HBV-positive and/or HIV-positive controls, and individuals unwilling to partake in the study. Liver diseases of alcoholic origin (for example alcoholic cirrhosis), metabolic liver diseases (for example NASH) confirmed by the hepatogastroenterologist of the CHU Campus Lomé are excluded from the study. Also were excluded individuals who did not provide explicit informed written consent.

All of these criteria are validated by the hepatogastroenterologist at the CHU Campus Lomé, who gives the green light for the collection of biological samples.

2.3. Sample Collection

Sampling began with interviews of patients using a structured questionnaire, collecting sociodemographic data, dietary habits, and history of liver disease. Following the interview, whole blood was collected into EDTA and dry labeled tubes for subsequent serological and molecular analyses. After centrifugation, the samples were decanted and stored at −20˚C pending analysis.

2.4. Extraction and Quantification

Genomic DNA extraction was performed at the laboratory of molecular biology and genetics (LABIOGENE) using the Rapid Salting -Out technique [28] [41]. The principle is based on cell lysis, protein digestion and precipitation, impurity washing, and DNA elution. DNA concentration and purity were measured using a Biodrop spectrophotometer.

2.5. Analysis of Biochemical, Serological and Virological Parameters

Alpha-fetoprotein levels were determined using the *Enzyme- Linked Fluorescent Assay.* (ELFA) on the VIDAS analyzer using commercial bioMérieux kits. The VIDAS® analyzers from bioMérieux are compact and automated immunoassay systems based on ELFA technology. Known for their robustness, they enable rapid and reliable single-use testing for emergency, infectious diseases, and immunochemistry applications, with a throughput of up to 90 tests per hour.

The determination of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (T-BIL), direct bilirubin (D-BIL), and gamma-glutamyl transpeptidase (GGT) levels was performed using commercial kits in a Cobas c311 analyzer (Roche Diagnostics GmbH, Sandhofer Strasse).The Cobas®c311 is an in vitro diagnostic medical device; a fully automated system for clinical chemistry and immunological analysis for the quantitative/qualitative in vitro determination of analytes in body fluids. The following are considered normal values: AST and ALT (M: 10 to 50 IU/L, F: 10 to 35 IU/L), GGT (M: 10 to 75 IU/L, F: 6 to 42 IU/L), AFP (<12 IU/mL), Bil-T (<12 mg/L), Bil-D (<2 mg/L).

Hepatitis B viral load was determined using the Cobas HBV Test. The Cobas HBV test is a quantitative nucleic acid assay performed on the Cobas® 4800 System using plasma from patients infected with HBV. Cobas® HBV is an in vitro nucleic acid amplification test for the quantitation of hepatitis B virus (HBV) DNA in human EDTA plasma of HBV-infected individuals. Viral load testing on the Cobas® 4800 System is based on fully automated sample preparation (nucleic acid extraction and purification) followed by PCR amplification and detection. Probes are used to detect and quantify HBV genotypes A, B, C, D, E, F, G, and H, as well as the main HBV precore mutant. The detection threshold is 10 UI/Ml.

2.6. Polymorphism Genotyping rs1800795 of the *IL6* Gene

Genotyping of the rs1800795 polymorphism was performed by PCR-RFLP [25] [28] [42] [43]. For this purpose, 20 µL reaction mixture was prepared containing, for each sample, 5 µL of DNA, 5 µL of FIREPol 5x "Master Mix Ready to Load", 0.5 µL of each primers [43] diluted 1/10 (**Table 1**) and 9 µL of H_2O was prepared for the conventional PCR. This PCR was performed under the following conditions: The initial denaturation of the IL6 gene was carried out at 94˚C for 5 min, followed by 35 cycles at 94˚C for 30 s (second denaturation), 58˚C for 45 s

Table 1. Primers sequences.

Polymorphisms	Primers	Expected size after amplification	Enzyme	Expected size after digestion
IL6 Rs1800795	F: 5'-TGA CTT CAG CTT TAC TCT TTG T-3' A: 5'-CTG ATT GGA AAC CTT ATT AAG-3'	198 bp	SfaNI	198 bps, 140 bp 58 bp

(hybridization), 72˚C for 45 s (elongation), and a final step at 72˚C for 7 min for the final extension.

For enzymatic digestion, the restriction enzyme SfaNI (New England Biolabs) [42] was used under the following conditions: nuclease-free H_2O: 9.5 µL, NEBuffer^{TM}r3.1 10X: 5 µL (diluted 1/10), PCR product: 10 µL, SfaNI enzyme: 0.5 µL for a total volume of 25 µL. The reaction volume was thoroughly mixed and then incubated at 37˚C for 1 hour and at 65˚C for 20 minutes to inhibit enzymatic activity. Human growth factor (HGF) was used for quality control of our PCRs during our experiments.

2.7. Statistical Analyses

Data were entered using Excel 2019 and analyzed using SPSS version 20 and EPI Info 7.2.5.0. The odds ratio (OR) was calculated for comparisons with a 95% confidence interval. Differences were considered statistically significant for a p-value < 0.05. As statistical tests taking into account the p-value, the uncorrected chi-square test is used for sample sizes greater than 5 and the two-tailed Fisher's exact test for sample sizes less than 5.

2.8. Ethical Considerations

- *Competent Authorities*

This study received approval from the Togolese Bioethics Committee for Health Research (Reference: Opinion No. 054/2023/CBRS of 22/11/2023). In the field, healthcare personnel at the study sites were informed of all aspects of the study, and participation was voluntary.

- *Participant consent*

Each participant signed an informed consent form presented to them by the research team. For participants unable to read the form, a translation of its content was provided in the local language in the presence of a witness. Prior to the signing, each participant or witness was informed of the study's purpose by reviewing a study information sheet.

- *Management of personal data*

A unique inclusion code was assigned to each participant by the investigator and recorded in a confidential register (Excel file). This document constitutes the sole identification key linking personal data (surname/first name) to inclusion numbers; kept and secured by the investigators, it guarantees the irreversible anonymization of the study data.

3. Results

3.1. Description of the Study Population

3.1.1. Depending on Age and Sex

The study population comprised a total of 146 participants, divided into 58 women (39.73%) and 88 men (60.27%). The age of the subjects ranged from 17 to 84 years, with a mean of 41.20 ± 14.17 years.

Analysis by sex shows that women had a mean age of 41.00 ± 13.63 years, slightly lower than that of men (41.33 ± 14.59 years).

Considering the clinical subgroups, the mean age was 36.83 ± 11.93 years in controls, 33.62 ± 10.94 years in patients with chronic hepatitis B (HCB), 46.34 ± 13.28 years in cirrhotics and 52.32 ± 14.92 years in patients with hepatocellular carcinoma (HCC).

These values reflect a trend towards increasing age with disease severity, suggesting that progression to advanced forms of HBV is more common in older subjects.

3.1.2. According to Clinical Status

Our study population consisted of 92 cases (HBC = 29; Cirrhosis = 41 and HCC = 22) and 54 controls. **Figure 1** shows the proportions of the subgroups of chronic hepatitis (19.86%), cirrhosis (28.08%), HCC (15.07%) and controls (36.99%) (**Figure 1**).

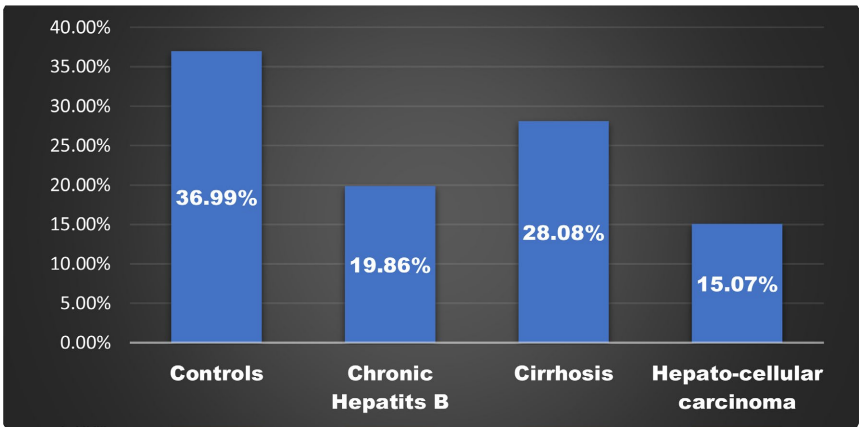


Figure 1. Distribution of the population according to clinical status.

3.2. Comparison of Genotypic and Allelic Frequencies of the IL6 Gene Polymorphism rs1800795 between Cases and Controls

3.2.1. Genotyping Strategy

The SfaNI polymorphism is due to the substitution of a guanine by a cytosine at position 174 [42] [43]. **Figure 2** shows the results obtained after UV detection of the PCR and digestion products. The PCR product bands are expected at 198 bp (**Figure 2(a)**). **Figure 2(b)** shows the different genotypes identified. Wells 1' and 2' show a single band at 198 bp for the CC genotype. Wells 1, 2, and 3 show two bands at 140 bp and 58 bp for the GG genotype, and wells 4, 5, and 6 show three

bands at 198 bp, 140 bp, and 58 bp for the CG genotype (**Figure (2b)**).

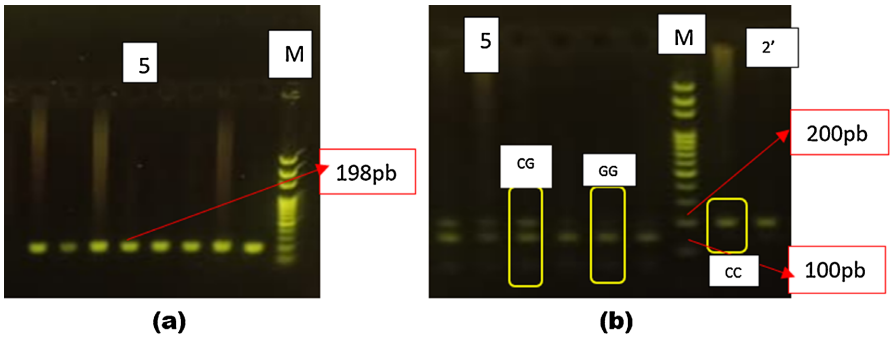


Figure 2. Electrophoresis gel products. Legend: (a) Electrophoresis gel of PCR products. (b) Electrophoresis gel of digestion products. M: Molecular weight marker; bp: even base.

3.2.2. Comparative Analysis of Observed and Predicted Genotypic Frequencies According to Clinical Status

According to the Hardy-Weinberg equilibrium principle, Table 2 highlights a slight difference between observed and predicted genotypic frequencies in both cases and controls (Table 2). The Hardy-Weinberg analysis revealed a significant disequilibrium in the case group ($p < 0.05$), while the control group maintained this balance ($p = 0.26$). The analysis also revealed a significant disequilibrium in the general population ($p < 0.05$). These differences constitute a probable Hardy-Weinberg disequilibrium, thus revealing the influence of various factors, such as natural selection, genetic drift, and the relatively small size of the sample studied.

Table 2. Comparison of expected and observed genotypic frequencies.

Genotypes	Case		Controls	
	Observed	Calculated	Observed	Calculated
GG	13	25	17	19
GC	70	46	30	26
CC	9	21	7	9
Total	92	92	54	54
HWE	p-value < 0.05		p-value > 0.05	
	p < 0.05 (Total population)			

3.2.3. Genotypic and Allelic Comparisons of the rs1800795 Polymorphism in Cases and Controls

The GG genotype and the G allele were used as a reference to assess the risk of progression to severe forms of hepatitis B virus infection. The distribution of genotypes and alleles between cases and controls is shown in Table 3. Genotypic frequencies were 9.78% for CC homozygotes, 76.09% for GC heterozygotes, and 14.13% for GG homozygotes in cases. In controls, these frequencies were 12.93% for CC homozygotes, 55.55% for GC heterozygotes, and 31.49% for GG homozygotes. The frequency of the wild-type G allele was 52.17% in cases and 59.26% in

controls, with no significant difference ($p > 0.05$). This distribution highlights a predominance of the heterozygous GC genotype, suggesting that the GC profile of the rs1800795 of the IL6 gene appears to be associated with a three times increased probability of progression to severe forms of HBV infection with trends almost at the limit of statistical significance (OR = 3.05; 95% CI: 1.31 - 7.06; p = 0.07) (Table 3).

Table 3. Genotypic and allelic frequencies in cases and controls.

			Total Pop N = 146 (%)	Case N = 92 (%)	Controls N = 54 (%)	OR (95% CI)	p-value
rs 1800795	Genotype	GG	30 (20.55)	13 (14.13)	17 (31.49)	**Reference**	
		GC	100 (68.49)	70 (76.09)	30 (55.55)	3.05 (1.31 - 7.06)	0.07
		CC	16 (10.96)	9 (9.78)	7 (12.93)	1.68 (0.49 - 5.71)	0.40
	Allele	G	160 (54.79)	96 (52.17)	64 (59.26)	**Reference**	
		C	132 (45.21)	88 (48.83)	44 (40.74)	1.33 (0.82 - 2.15)	0.24

OR: Odds ratio IC: Confidence interval.

3.3. Genotypic and Allelic Frequencies of the IL6 Gene rs1800795 Polymorphism Stratified by Sex

- **In women:** Genotypic frequencies were 7.50%, 77.5%, and 15.0% for CC, GC, and GG genotypes, respectively, in cases, and 16.67%, 50.0%, and 33.33% for CC, GC, and GG genotypes, respectively, in controls. The frequency of the G allele was 53.75% in cases and 58.33% in controls. This analysis shows that the GC genotype is the most prevalent and appears to be associated with the development of severe forms of the disease, with a difference of significance at the threshold (OR = 3.44; 95% CI: 0.89 - 13.33; p = 0.06) (Table 4).
- **In men:** The GC genotype has the highest genotypic frequency at 75.0% in cases and 58.53% in controls. This is followed by the GG genotype, at 13.46% and 30.55% in cases and controls, respectively. The CC genotype is the least frequent at 11.54% and 11.12% in cases and controls. The frequency of the G allele was 50.96% in cases and 59.72% in controls. In men, the GC genotype nearly triples the risk of developing severe forms of HBV infection in Togo, with a statistically significant difference (OR = 2.91; 95% CI: 0.98 - 8.64; p = 0.04) (Table 4).

3.4. Comparison of Genotypic and Allelic Frequencies of the rs1800795 Polymorphism of the IL6 Gene between the Different Clinical Subgroups

Taken in isolation, comparative analysis between clinical subgroups (controls, HBC, cirrhosis and HCC) according to genotypic and allelic frequencies revealed interesting results allowing us to have a better idea of the action of the rs1800795 polymorphism of the IL6 gene during the evolution of an HBV infection (Table 5).

Table 4. Distribution of genotypic and allelic frequencies of the IL6 gene rs1800795 polymorphism according to sex.

		Women				Man			
		Case N = 40 (%)	Controls N = 18 (%)	OR (95% CI)	*p -value*	Case N = 52 (%)	Controls N = 36 (%)	OR (95% CI)	p-value
rs 1800795									
Genotype	GG	6 (15.0)	6 (33.33)	**Reference**		7 (13.46)	11 (30.55)	**Reference**	
	GC	31(77.5)	9 (50.0)	3.44(0.89 - 13.33)	0.06	39 (75.00)	21 (58.33)	2.91 (0.98 - 8.64)	0.04
	CC	3 (7.5)	3 (16.67)	1.00 (0.14 - 7.09)	0.69	6 (11.54)	4 (11.12)	2.35 (0.48 - 11.45)	0.24
Allele	G	43 (53.75)	21 (58.33)	**Reference**		53 (50.96)	43 (59.72)	**Reference**	
	C	37 (46.25)	15 (41.67)	1.20 (0.54 - 2.66)	0.64	51 (49.04)	29 (40.28)	1.42 (0.77 - 2.62)	0.25

OR = Odds Ratio CI = Confidence Interval.

Table 5. Genotypic and allelic frequencies of the rs1800795 polymorphism of the IL6 gene between the different clinical subgroups.

Genotypic and allelic frequencies in HBC and cirrhosis						
			HBC N = 29 (%)	Cirrhosis N = 41 (%)	OR (95% CI)	p-value
rs 1800795	Genotype	GG	5 (17.24)	6 (14.63)	Reference	
		GC	21 (72.41)	32 (78.05)	1.26 (0.34 - 4.69)	0.72
		CC	3(10.35)	3 (7.32)	0.83 (0.11 - 6.11)	0.62
	Allele	G	31 (53.45)	44 (53.66)	Reference	
		C	27 (46.55)	38 (46.34)	0.99 (0.50 - 1.94)	0.98
Genotypic and allelic frequencies in HBC and controls						
			HBC N = 29 (%)	Controls N = 54 (%)	OR (95% CI)	p-value
rs 1800795	Genotype	GG	5 (17.24)	17 (31.49)	Reference	
		GC	21 (72.41)	30 (55.55)	2.38 (0.75 - 7.46)	0.13
		CC	3 (10.35)	7 (12.96)	1.45 (0.27 - 7.82)	0.48
	Allele	G	31 (53.45)	64 (59.26)	**Reference**	
		C	27 (46.55)	44 (40.74)	1.26 (0.66 - 2.41)	0.47
Genotypic and allelic frequencies in HCC and cirrhosis						
			HCC N = 22 (%)	Cirrhosis N = 41 (%)	OR (95% CI)	p-value
rs 1800795	Genotype	GG	2 (9.10)	6 (14.63)	**Reference**	
		GC	17 (77.27)	32 (78.05)	1.59 (0.28 - 8.76)	0.46
		CC	3 (13.63)	3 (7.32)	3.0 (0.31 - 28.84)	0.34
	Allele	G	21 (47.72)	44 (53.66)	**Reference**	
		C	23 (52.28)	38 (46.34)	1.26 (0.60 - 2.64)	0.52

Continued

Genotypic and allelic frequencies in HBC and HCC						
			HBC N = 29 (%)	HCC N = 22 (%)	OR (95% CI)	p-value
rs 1800795	Genotype	GG	5 (17.24)	2 (9.10)	**Reference**	
		GC	21 (72.41)	17 (77.27)	2.02 (0.34 - 11.76)	0.35
		CC	3 (10.35)	3 (13.63)	2.50 (0.25 - 24.72)	0.41
	Allele	G	31 (53.45)	21 (47.72)	**Reference**	
		C	27 (46.55)	23 (52.28)	1.25 (0.57 - 2.75)	0.56
Genotypic and allelic frequencies in HCC and Controls						
			HCC N = 22 (%)	Controls N = 54 (%)	OR (95% CI)	p-value
rs 1800795	Genotype	GG	2 (9.10)	17 (31.49)	**Reference**	
		GC	17 (77.27)	30 (55.55)	4.81 (0.99 - 23.41)	0.03
		CC	3 (13.63)	7 (12.96)	3.64 (0.49 - 26.75)	0.20
	Allele	G	21 (47.72)	64 (59.26)	**Reference**	
		C	23 (52.28)	44 (40.74)	1.59 (0.78 - 3.22)	0.19
Genotypic and allelic frequencies in cirrhosis and control groups						
			Cirrhosis N = 41 (%)	Controls N = 54 (%)	OR (95% CI)	p-value
rs 1800795	Genotype	GG	6 (14.63)	17 (31.49)	**Reference**	
		GC	32 (78.05)	30 (55.55)	3.02 (1.05 - 8.68)	0.03
		CC	3 (7.32)	7 (12.96)	1.21 (0.23 - 6.27)	0.56
	Allele	G	44 (53.66)	64 (59.26)	**Reference**	
		C	38 (46.34)	44 (40.74)	0.92 (0.50 - 1.70)	0.80

OR: Odds ratio IC: Confidence interval.

HBC vs. Cirrhosis: Following this analysis, the CC genotype and the G allele revealed a protective tendency against HBV infection towards severe forms; although this association was not statistically significant overall ($p > 0.05$). As for the GC genotype, a non-significantly increased probability of progression to severe forms of the infection appeared to be associated (OR = 1.26; 95% CI: 0.34 - 4.69; $p = 0.72$).

Controls vs HBC, Cirrhosis vs HCC and HBC vs HCC: From this analysis, it seems revealed that the genotypes and alleles of the rs1800795 polymorphism confer a non-statistically significant positive risk in all of these comparisons so could be considered as a risk factor (OR > 1; $p > 0.05$).

Controls vs. cirrhosis: Although no significant association (OR < 1, $p > 0.05$) was identified, the C allele appears to confer a reduced risk of progression to cir-

rhosis. Conversely, the GC and CC genotypes reveal a high risk (OR > 1; p > 0.05). The GC genotype specifically increases the risk of developing liver cirrhosis threefold (OR = 3.02; 95% CI: 1.05 - 8.68; p = 0.03).

Controls vs. HCC: In this scenario, the genotypes (GC and CC) and the C allele were associated with a positive risk of developing complications related to HBV infection (OR > 1). The GC heterozygote stands out as a statistically significant risk factor, increasing the risk of developing hepatocellular carcinoma fourfold (OR = 4.81; 95% CI: 0.99 - 23.41; p = 0.03).

These analyses, resulting in conclusive observations, highlight the importance of studying the rs1800795 polymorphism of the IL6 gene; of better understanding the influence of this genetic factor in the progression of HBV infections and their potential implications in prognosis.

3.5. Genotypic and Allelic Frequencies of the rs1800795 Polymorphism of the IL6 Gene between the Different Biochemical, Immuno-Serological and Virological Parameters

To better understand the relationship between certain biochemical parameters (aspartate aminotransferases (AST), alanine aminotransferases (ALT), total bilirubin (T-BIL), direct bilirubin (D-BIL), gamma-glutamyl transpeptidase (GGT)), immunoserological parameters (alpha-fetoprotein (AFP)), and virological parameters (hepatitis B viral load) and the IL6 gene polymorphism rs1800795, a comparative analysis was performed to determine the association between these parameters and genotypic and allelic frequencies. This analysis revealed interesting results, providing a precise understanding of the action of the IL6 gene polymorphism rs1800795 in relation to biochemical, immunoserological, and virological parameters during the progression of HBV infection.

3.5.1. Based on Biochemical and Immuno-Serological Parameters

Biochemical (AST, ALT, Bil-T, Bil-D, GGT) and immuno-serological (AFP) analyses were performed on 140 participants consisting of controls (all persons free from any viral pathology), patients with chronic hepatitis B, liver cirrhosis B, and hepatocellular carcinoma (Table 6).

Based on AST, Bil-T, Bil-D, GGT, and AFP: This analysis appears to reveal that the genotypes and alleles of the rs1800795 polymorphism confer a positive, but not statistically significant, increased risk across all comparisons. The increase in AST, Bil-T, Bil-D, GGT, and AFP... could be considered a risk factor for the development of HBV infection (OR > 1, p > 0.05).

Depending on the ALAT: Although no significant association (OR < 1, p > 0.05) was identified, the GC genotype and the C allele appear to confer a reduced risk. Increased ALT levels appear to have no effect on the progression of HBV infection to severe forms, taking into account the IL6 gene polymorphism rs1800795.

3.5.2. Based on Virological Parameters (Hepatitis B Viral Load)

A total of 92 viral load tests were performed on patients who tested positive for

Table 6. Genotypic and allelic frequencies of the rs1800795 polymorphism of the IL6 gene between different biochemical and immuno-serological parameters.

Genotypic and allelic frequencies according to aspartate aminotransferases (AST)						
			Pathological value N = 78 (%)	Normal value N = 62 (%)	OR (95% CI)	p-value
rs 1800795	Genotype	GG	13 (16.67)	14 (22.58)	Reference	
		GC	56 (71.79)	42 (67.74)	1.43 (0.61 - 3.37)	0.40
		CC	9 (11.54)	6 (9.68)	1.62 (0.44 - 5.80)	0.46
	Allele	G	82 (52.56)	70 (56.45)	Reference	
		C	74 (47.44)	54 (43.55)	1.16 (0.72 - 1.87)	0.51
Genotypic and allelic frequencies according to alanine aminotransferases (ALT)						
			Pathological value N = 11 (%)	Normal value N = 129 (%)	OR (95% CI)	p-value
rs 1800795	Genotype	GG	3 (27.27)	24 (18.60)	Reference	
		GC	8 (72.73)	90 (69.77)	0.71 (0.17 - 2.88)	0.43
		CC	0 (00.00)	15 (11.63)	N/A	0.25
	Allele	G	14 (63.64)	138 (53.49)	**Reference**	
		C	8 (36.36)	120 (46.51)	0.65 (0.26 - 1.62)	0.35
Genotypic and allelic frequencies according to Alpha-fetoproteins (AFP)						
			Pathological value N = 61 (%)	Normal value N = 79 (%)	OR (95% CI)	p-value
rs 1800795	Genotype	GG	9 (14.75)	18 (22.78)	**Reference**	
		GC	45 (73.77)	53 (67.09)	1.69 (0.69 - 4.14)	0.24
		CC	7 (11.48)	8 (10.13)	1.75 (0.48 - 6.37)	0.39
	Allele	G	63 (51.64)	89 (56.33)	**Reference**	
		C	59 (48.36)	69 (43.67)	1.20 (0.75 - 1.94)	0.43
Genotypic and allelic frequencies as a function of total bilirubin (Bil-T)						
			Pathological value N = 73 (%)	Normal value N = 67 (%)	OR (95% CI)	p-value
rs 1800795	Genotype	GG	13 (17.81)	14 (20.88)	**Reference**	
		GC	52 (71.23)	46 (68.66)	1.21 (0.51 - 2.85)	0.65
		CC	8 (10.96)	7 (10.46)	2.50 (0.25 - 24.72)	0.41
	Allele	G	78 (53.42)	74 (55.22)	**Reference**	
		C	68 (46.58)	60 (44.78)	1.07 (0.67 - 1.72)	0.76
Genotypic and allelic frequencies according to direct bilirubins (Bil-D)						
			Pathological value N = 89 (%)	Normal value N = 51 (%)	OR (95% CI)	p-value
rs 1800795	Genotype	GG	14 (15.73)	13 (25.49)	**Reference**	

Continued

		GC	64 (71.91)	34 (66.67)	1.74 (0.73 - 4.13)	0.20
		CC	11 (12.36)	4 (7.84)	2.55 (0.64 - 10.05)	0.15
	Allele	G	92 (51.69)	60 (58.82)	**Reference**	
		C	86 (48.31)	42 (41.18)	1.33 (0.81 - 2.18)	0.24
Genotypic and allelic frequencies according to Gamma-glutamyl transpeptidase (GGT)						
			Pathological value N = 65 (%)	Normal value N = 75 (%)	OR (95% CI)	p-value
rs 1800795	Genotype	GG	11 (16.92)	16 (21.33)	**Reference**	
		GC	47 (72.31)	51 (68.00)	1.34 (0.56 - 3.18)	0.50
		CC	7 (10.77)	8 (10.67)	1.27 (0.35 - 4.54)	0.71
	Allele	G	69 (53.08)	83 (55.33)	**Reference**	
		C	61 (46.92)	67 (44.67)	1.09 (0.68 - 1.75)	0.70

OR: Odds ratio, CI: Confidence interval, NA: Not Applicable, Pathological value: value not within the normal range, Normal value: value between standard values.

chronic hepatitis B, liver cirrhosis B, and hepatocellular carcinoma. Following this analysis, the GC genotype appeared to show a protective tendency against severe forms of HBV infection based on viral load; however, this association was not statistically significant overall (OR = 0.59; 95% CI: 0.17 - 1.98; p = 0.39). Conversely, the CC genotype and the C allele revealed a statistically non-significantly high risk (OR > 1; p > 0.05). Taken individually, the CC genotype appears to increase the risk of developing a severe form of HBV infection fivefold (OR = 5.0; 95% CI: 0.47 - 52.96; p = 0.17) (Table 7).

Table 7. Genotypic and allelic frequencies of the IL6 gene rs1800795 polymorphism as a function of viral load.

Genotypic and allelic frequencies according to viral load (N = 92)					
		Detectable viral load N = 50 (%)	Undetectable viral load N = 42 (%)	OR (95% CI)	p-value
Genotype	GG	8 (16.00)	5 (11.91)	**Reference**	
	GC	34 (68.00)	36 (85.71)	0.59 (0.17 - 1.98)	0.39
	CC	8 (16.00)	1 (2.38)	5.0 (0.47 - 52.96)	0.17
Allele	G	50 (50.00)	46 (54.76)	**Reference**	
	C	50 (50.00)	38 (45.24)	1.21 (0.67 - 2.16)	0.51

OR: Odds ratio, CI: Confidence interval, Detection threshold at 10 UI/mL.

4. Discussion

The first study of its kind in West Africa, specifically in Togo, allowed us not only to estimate the allelic and genotypic frequencies of the IL6 gene polymorphism rs1800795 within our study population (comprising healthy HBV carriers (con-

trols) and patients with a clinical form of the infection, namely chronic hepatitis B (HBV), cirrhosis, and hepatocellular carcinoma (HCC)), but also to assess their impact on the progression of HBV infection. It should be noted that very few studies have addressed this topic; this is a first in sub-Saharan Africa.

Of the 146 participants in this study, the mean age was 41.20 ± 14.17 years, with a significantly higher proportion of male participants (60.27%) than female participants (39.73%). Depending on clinical status, age increased progressively with disease severity, ranging from 33.62 ± 10.94 years in patients with chronic hepatitis B (HCB) to 46.34 ± 13.28 years in those with cirrhosis, and then to 52.32 ± 14.92 years in patients with hepatocellular carcinoma (HCC). This gradual increase in age reflects a trend toward severe forms of disease in older individuals. This suggests that adults with weakened immune systems can easily allow the virus to spread. Taken individually, for example, the average age of patients with cirrhosis was 46.34 ± 13.28 years. Our results are close to previous studies conducted at the Yalgado Ouédraogo University Hospital Center, which found average ages of cirrhosis patients of 46.5 and 46.9 years in 2002 and 2020, respectively [44] [45]. However, our results differ from those of a study conducted in America, where the average age was approximately 60 years [46]. These figures show that our patients were younger compared to those in developed countries. The age difference observed between our West African population (predominance of viral liver infections) and the American population (predominance of the risk factor alcohol) could be explained by the etiology of cirrhosis (the same applies to the average age of patients with HCC in our study population, compared to that of developed countries).

In the present study, the genotypic frequency of the IL6 gene polymorphism rs1800795: GG, GC, and CC were 14.13%, 76.09% and 9.78% respectively in cases and 31.49%, 55.55% and 12.93% in controls. The frequency of the wild-type allele G was 52.17% in cases and 59.26% in controls, with no significant difference ($p > 0.05$). In the general population, it is as follows: 20.55% for the GG genotype, 68.49% for the GC genotype, and 10.96% for the CC genotype; the frequency of the G allele was 54.79% and that of the C allele is 45.21%. This distribution highlights a predominance of the heterozygous GC genotype, suggesting that the GC profile of the rs1800795 of the IL6 gene appears to be associated with a threefold increased probability of progression to severe forms of HBV infection, with trends almost at the limit of statistical significance (OR = 3.05; 95% CI: 1.31 - 7.06; $p = 0.07$). Our results corroborate those found by Sedykh *et al.,* in a Russian study on the analysis of certain polymorphic variants of the IL-6 and IL-10 genes in individuals with psychoneurological manifestations of COVID. They found a predominance of the heterozygous GC genotype in the study group (69.23% vs. 50%; $p = 0.0032$) [47]. Our results are also similar to those found by Lan *et al.,* in their review on the involvement of IL-6 in HBV evolution, who found that in Caucasian and Indian populations, the frequency of the C allele (−174G > C) is between 0.4 and 0.55, while in African Americans, it is between 0.5 and 0.9 [1] [48]. From these

results, we can conclude that the frequency of genotypes and alleles varies considerably according to race and ethnic groups. This can be explained by the genetic factors of each ethnic group, its geographic location, and its climatic exposures.

The polymorphic analysis of rs1800795 by sex reveals interesting results. In women, the GC genotype is the most prevalent and appears to be associated with the development of severe forms of the disease, with a difference of significance at the threshold (OR = 3.44; 95% CI: 0.89 - 13.33; p = 0.06). In men, the GC genotype nearly triples the risk of developing severe forms of HBV infection in Togo, with a significant difference (OR = 2.91; 95% CI: 0.98 - 8.64; p = 0.04). These two analyses suggest that men may have a genetic predisposition that facilitates the development of hepatitis B infection to severe forms. This could also be explained by hormonal effects and various exposures (physical labor, UV radiation, etc.). For example, the virus's genome contains a particular DNA sequence that interacts with the androgen receptor. This could explain why men infected with the virus are likely to develop severe forms of the infection [49]-[51].

Comparative analysis between clinical subgroups (controls, HBC, cirrhosis, and HCC) based on genotypic and allelic frequencies provided a clear understanding of the impact of the IL6 gene polymorphism rs1800795 during the progression of HBV infection. Following this comparison, a major risk factor for the progression of HBV infection to severe forms was statistically significantly associated with the GC genotype of rs1800795 in the subgroup of healthy subjects to liver cirrhosis (OR = 3.02; 95% CI: 1.05 - 8.68; p = 0.03) and to hepatocellular carcinoma (OR = 4.81; 95% CI: 0.99 - 23.41; p = 0.03). Our results are similar to those of Verma. *et al.,* where individuals carrying the GC genotype of the IL6 polymorphism (−174G > C) had a significantly higher risk of severe COVID-19 [OR: 3.86; p < 0.001] [52]. Our results also corroborate findings from Kaol *et al.,* and Galun *et al.,* who support the idea that interleukin-6 shows a statistically significant correlation in patients with advanced liver disease and in patients with HCC in their studies in China and Israel, respectively [53] [54]. Our results are similar to the results of an American study found by Ognjanovic *et al.,* on cytokines and hepatocellular carcinoma. They found that T helper (Th) 1 genes (*IFNγ, IL-6,* and *IL-12*) were associated with statistically non-significant increases in the risk of HCC [55]. In contrast, our results do not corroborate those found by Park *et al.,* who appear not to have found a significant relationship between IL-6 genetic variants and the development of cirrhosis and hepatocellular carcinoma from chronic HBV infection in Koreans and Caucasians. [56]. Several attempts to characterize IL6 gene polymorphisms in infection progression have failed to provide conclusive data on the role of IL 6 (174G/C) [2]; this is the case of Akahane *et al.,* in Japan [57] and Ribeiro *et al.,* in Brazil [58].

Several hypotheses can explain and support our results: First, naturally occurring IL-6 plays an important role in protecting the liver during T-cell-mediated liver injury, including hepatitis [55]. It inhibits apoptosis, promotes liver regeneration, and protects against a multitude of harmful influences on the liver. Xia *et*

al. showed that the virus, the immune response, and genetic diversity are the three main factors influencing the course of HBV infection [2]. A significant gene mutation within the rs1800795 polymorphism of the IL-6 gene would lead to gene disruption, loss of functionality, and complete disorganization of the gene structure. This gene restructuring, along with other environmental factors (climatic and geographic exposures, exposure to mutagenic substances, UV radiation, dietary habits, race, and ethnicity), would explain why the heterozygous GC-mutant genotype is a risk factor for the development of severe forms of HBV infection. Secondly, a subsequent study demonstrated that the single nucleotide polymorphism (SNP) −174G/C in the IL-6 promoter region increased IL-6 transcription and expression, and that serum IL-6 levels were associated with the progression of hepatitis B-related hepatocellular carcinoma (HCC) [55]. IL-6 levels are frequently elevated in patients with hepatitis B, and persistent IL-6 exposure can lead to liver damage, potentially resulting in hepatocellular carcinoma (HCC). Therefore, inhibiting IL-6 signal transduction could represent an innovative therapeutic strategy for hepatitis B-associated HCC [2]. Third, clinical and epidemiological studies have shown that inflammation plays an important role in tumor initiation and progression [59]. Hepatocellular carcinoma (HCC) is an example of an inflammation-linked cancer, which may be partly triggered by exposure to infectious agents such as hepatotropic viruses. Furthermore, IL-6 is considered one of the molecules that link inflammation and cancer [60].

Overall, comparative analysis of genotypes and alleles of the IL6 gene rs1800795 polymorphism according to regularly measured liver parameters shows an increase in AST, Bil-T, Bil-D, GGT, AFP, and viral load These could be considered a risk factor for the development of HBV infection [61], although these associations remain statistically insignificant across all comparisons ($OR > 1$, $p > 0.05$). We found no studies specifically linking these liver parameters to the IL6 gene rs1800795. Our results are consistent with several studies that have shown a significant increase ($p \leq 0.05$ - 0.001) in these biochemical parameters in patients with hepatitis B, thus identifying risk factors associated with hepatitis progression and liver damage [2] [62] [63]. This increase is explained by the fact that these are molecules with a direct link to the liver, either produced by the liver or acting directly on the liver. Given that the hepatitis virus causes liver inflammation, it follows that these various molecules are found to be elevated. In our study, only ALT appears to have no significant association ($OR < 1$, $p > 0.05$) with an opposing effect with the other liver parameters listed above. For some authors, even with normal ALT, elevated AST and GGT, associated with viral load, predict significant liver inflammation [64]. A moderate to high viral load is an independent risk factor for significant inflammation, even with normal ALT [65].

5. Study Limitations

The main limitation of our study lies in the sampling process. Due to a lack of information or awareness, almost all patients are admitted to the hepato-gastro-

enterology department at very advanced stages of the disease (with death occurring within a maximum of 24 hours of admission) with medical records that are often incomplete or even empty due to late admission and the patient being in a comatose state. Secondly, the frequency of cases was relatively low (barely three patients per week, and even then, inclusion and exclusion criteria had to be applied). Finally, a lack of financial resources prevented us from considering alternative sample collection strategies, such as visiting all hospitals in Togo with hepato-gastro-enterology departments.

6. Conclusion

Our study determined the allelic and genotypic frequencies of the IL6 gene polymorphism rs1800795 and their involvement in the occurrence of complications from HBV infection in the Togolese population. From a genetic standpoint, the GG, GC, and CC genotypic frequencies of the rs1800795 polymorphism were 20.55%, 68.49%, and 10.96%, respectively. The frequency of the G allele was 54.79% and that of the C allele is 45.21%. From these analyses, this study showed that a potential risk factor for the occurrence and progression to severe forms of HBV infection was statistically significantly associated with the GC genotype of the rs1800795 polymorphism of the IL6 gene, specifically in the subgroup of healthy carriers, leading to liver cirrhosis and hepatocellular carcinoma. These analyses, resulting in conclusive observations, highlighted the importance of studying the rs1800795 polymorphism of the IL6 gene and allowed for a better understanding of the influence of this genetic factor on the progression of HBV infections and their potential prognostic effects. Nevertheless, it is important to consider certain biochemical parameters (quantitative serum levels of IL-6, procalcitonin, and C-reactive protein), clinical parameters (treatment and monitoring), and environmental parameters (exposures) in order to further conduct scientific research and better understand and identify other factors that may contribute to the development of severe forms of the disease. This would help identify new therapeutic targets, promote the development of new anti-hepatitis drugs and liver biomarkers, and guide clinicians in the management of severe cases, particularly in high-prevalence regions such as Togo.

Statement Regarding Data Availability and Sharing

The data used and/or analyzed during this study are available from the corresponding author upon reasonable request.

Ethical Statement

This study has received approval from the Togolese Bioethics Committee for Health Research (Reference: Opinion No. 054/2023/CBRS of 22/11/2023).

Information about Consent

Our study complies with the Declaration of Helsinki, adopted by the World Med-

ical Association (WMA), on the ethical principles governing medical research involving human subjects. Participants gave their free and informed consent. Every effort was made to preserve not only the privacy, but also the confidentiality, dignity, and honor of the patients.

Author Contributions

Concept and design of the study: LT, KSD, FWD and JS.

Sampling and laboratory analyses: LT, SFD, KD, LLM, NLK, FL, KIMLT, KS, TL, KSD, FWD and JS.

Statistical analysis and interpretation of data: LT, KIMLT and KS.

Manuscript written by: LT, KIMLT and KS.

Critical review of the manuscript for intellectual content: FL, OD, NBM, KSD, FWD and JS.

Administrative, technical and material support: LT, KSD, FWD and JS.

The corresponding author states that the manuscript has been read and approved by all the named authors and that the order of authorship in the manuscript has been approved by all of us.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

CHB	Chronic Hepatitis B
DNA	Deoxyribonucleic Acid
IL6	Interleukin 6
HBsAg	HBs Antigen
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HSC	Hepatic stellate cells
KIR	Killer cell immunoglobulin-like receptor
WHO	World Health Organization
p53	Tumor protein 53
RB1	Retinoblastoma 1
rs	SNP reference
SNP	Single nucleotide polymorphism
TGF-β1	Transforming growth factor-beta 1