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Involvement of *CD40* (rs1883832) and *MAP3K14* (rs2074292) Genes Polymorphisms in Hepatitis B Virus Infection in Burkina Faso, West Africa

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Abstract

Introduction: Hepatic diseases comprise inflammations of the liver, which can originate from drug-induced, toxic, autoimmune sources and particularly hepatitis B and C virus infection. The outcome of the disease is linked to interactions between the immune system and the virus, and also depends on the age and immune status of the patient. The aim of this study was to evaluate the association of a *MAP3K14* (rs2074292), *CD40* (rs1883832) polymorphism and chronic hepatitis B virus carriage in a population from Burkina Faso. **Methods:** In this case-control analysis, 223 and 173 samples, consisting of 90 and 53 controls and 133 and 120 cases, were examined for *MAP3K14* and *CD40* respectively. The cases included patients with Chronic Hepatitis B (CHB), cirrhosis or hepatocellular carcinoma (HCC). Genomic DNA extraction was executed using INVITROGEN and FAVORGEN kits. Genotyping of *MAP3K14* (rs2074292) and *CD40* (rs1883832) gene polymorphisms was accomplished via real-time PCR on the QuantStudioTM 5 Real-Time instrument, followed by allelic discrimination using TaqMan Genotyper Software. Data was interpreted using SPSS version 20 and Epi info version 7.5.2.0. Odds ratios (OR), confidence intervals (CI), and p-values were derived for risk and

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significance evaluation. **Results:** This study showed that the heterozygous CT genotype and the mutated T allele of the *CD40* (rs1883832) gene are involved in the progression of chronic hepatitis to cirrhosis and hepatocellular carcinoma in HBV-infected patients. However, no association was found between polymorphisms in the *MAP3K14* gene (rs2074292) and the progression of HBV infection. By combining the two polymorphisms, we observed either high risk or protection, depending on the genotypes of the *MAP3K14* and *CD40* genes simultaneously carried by the patient. **Conclusion:** Polymorphisms of the *MAP3K14* and *CD40* genes are associated with the evolution of HBV infection.

Keywords

Polymorphisms, *MAP3K14*, *CD40*, HBV and Burkina Faso

1. Introduction

Hepatic diseases are due to the inflammation of the liver, which can originate from viral, drug-induced, toxic, or autoimmune sources. Notably, viral hepatitis, a significant subset of hepatic diseases, presents a global public health challenge, impacting millions of individuals annually [1] [2]. Among these, viral hepatitis B and C stand out as the leading to liver damage with the potential progression to cirrhosis or liver cancer in sub-Saharan Africa and South-east Asia [2].

According to a 2014 report by the World Health Organization (WHO), viral hepatitis accounts for 1.4 million deaths each year, comparable to 1.6 million deaths from HIV/AIDS, 1.3 million from tuberculosis, and 600,000 from malaria. This report also highlights that approximately 2 billion people have been infected with the hepatitis B virus [3]. Additionally, Africa has the highest prevalence of HBV infection among children under five years of age, and 70% of new infections worldwide occur in the African region [4]. HBV and HCV strains of hepatitis notably contribute to substantial mortality and morbidity [3]. In West Africa, hepatitis B is endemic, with a prevalence of 8%, the highest worldwide [5]. Additionally, approximately 2% of the region's population carries chronic hepatitis C [5]. Burkina Faso, a West African country, is highly affected by HBV infection, with an estimated national prevalence of (12% - 14.5%) and lower prevalence of HCV (1% - 2.8%) [6]. Chronic hepatitis significantly escalates the risk of cirrhosis and primary liver cancer, which claim 900 and 1300 lives annually in the country, respectively [7].

The outcome of the disease is linked to interactions between the immune system and the virus, and also depends on the age and immune status of the patient. Indeed, in more than 90% of cases, adults infected with HBV have developed acute hepatitis and were able to control and eliminate the virus without long-term effects [8]. However, in 10% of cases, certain adults who are unable to fight the infection develop a chronic infection that can involve in the long term

into cirrhosis and/or hepatocellular carcinoma (HCC). Less than 1% of patients infected with HBV develop fulminant hepatitis which leads to their death in the absence of liver transplantation [8].

The progression towards chronicity depends on the interaction between viral factors and host factors, such as the immune status of the individual [7].

MAP3K14, is a widely expressed 947 amino acids, approximately 100 kDa cytoplasmic protein of the MAP kinase family, located on chr17. The gene of the same name encodes mitogen-activated protein kinase 14, NIK (NF kappa B inducing kinase), which is a serine/threonine protein kinase [9] [10]. This kinase binds to TNF receptor-associated factor 2 (TRAF2) and stimulates NF-κB activity. It is a critical kinase in the alternative NF-κB activation pathway. It shares sequence similarity with several other MAPKK [10]. In 2022, a Chinese study showed that the *MAP3K14* rs2074292 allele may have a potential predictor of HBV-HCC survival probably regulating *MAP3K14* mRNA expression [11]. The *MAP3K14* rs2074292 variant therefore has an impact on the evolution of HBV infection.

CD40 is a 40 kDa type I glycoprotein, a member of the nerve growth factor/tumor necrosis factor receptor family. It is found on many cell types, including B lymphocytes, dendritic and follicular cells, macrophages, hematopoietic progenitors, endothelial and epithelial cells, fibroblasts, and carcinoma cells [12]. *CD40* is expressed on B lymphocytes and antigen-presenting myeloid cells and plays an important role in the antiviral immune response. Studies have reported that *CD40* could be activated during viral infection and its activation could increase the antiviral capacity of its host. The Chronic Hepatitis B (CHB) susceptibility study indicates that significantly induced elevated *CD40* concentration in CHB patients was observed compared to healthy controls. Non-HLA region genes, such as *CD40*, may play an important role in chronic hepatitis B (CHB) [13].

A comprehensive understanding of these viral, host and environmental factors is essential for prevention and effective treatment to reduce the burden of HBV-related complications. To date, several genome-wide association studies (GWAS) of HCC have discovered SNPs associated with cancer risk and survival [14] [15]. There are few studies on polymorphisms on the involvement of *MAP3K14* and *CD40* genes in the occurrence and progression of B viral infection, particularly in Burkina Faso. Thus, in this study we evaluated the association of a *MAP3K14* (rs2074292) and *CD40* (rs1883832) polymorphism and chronic hepatitis B virus carriage in a population from Burkina Faso.

2. Material and Methods

2.1. Study Design, Setting, and Population

An analytical case-control study was undertaken between August and December 2022 in Ouagadougou, the capitol of Burkina Faso. The study enrolled two distinct cohorts: cases and controls. The case cohort consisted of individuals diag-

nosed with chronic hepatitis B (CHB), viral cirrhosis, and hepatocellular carcinoma attributed to HBV infection. Conversely, the control cohort included individuals tested negative for HBsAg, anti-HCV and HIV. Of the 223 study participants, there were 133 patients infected with HBV, including 48 cases of hepattocellular carcinoma, 16 cases of cirrhosis and 69 cases of chronic hepatitis B, and 90 healthy controls for *MAP3K14* (rs2074292) and on the 173 participants in the study including 120 cases consisting of 59 cases of chronic hepatitis B, 15 cases of cirrhosis, 46 cases of hepatocellular carcinoma and 53 controls for *CD40* (rs1883832). Participants with hepatocellular carcinoma and cirrhosis were recruited from the hepato-gastroenterology departments of Yalgado OUEDRAOGO (CHU-YO) teaching hospital and Paul VI hospital. Meanwhile, CHB participants were recruited from the Biomolecular Research Center Pietro Annigoni (CERBA) and the control groups from the National Blood Transfusion Center (CNTS).

2.2. 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, CT scan findings, and/or histological liver examination. Only individuals with HBV as the sole exposure factor were considered.
- Control group: participants tested negative for HBsAg, anti-HCV and HIV were categorized as controls.

2.3. Non-Inclusion Criteria

Encompassed HBV-negative cases, HIV-positive cases, HBV-positive and/or HIV-positive controls and individuals unwilling to participate to the study have been excluded. Also excluded were individuals who did not provide explicit informed written consent.

2.4. Sample Collection

Sampling began with patient interview employing a structured questionnaire, capturing socio-demographic data, dietary inclinations, and liver disease history. Subsequent to the interview, whole blood was collected and stored into two labeled tubes (EDTA and dry tube) for subsequent serological and molecular analyses. Following centrifugation, samples were stored at −20˚C waiting for analysis.

2.5. DNA Extraction and Quantification

Genomic DNA extraction was done using INVITROGEN and FAVORGEN kits by following the manufacturers' guidelines. DNA concentration and purity were

verified using the "Biodrop" spectrophotometer.

2.6. Genotyping of *MAP3K14* and *CD40* Genes Polymorphisms

Real-time PCR was done by using the QuantStudioTM 5 Real-Time PCR System for the genotyping of the *MAP3K14* (rs2074292) and *CD40* (rs1883832) gene polymorphisms. Each genotyping reaction (25 µL total volume) consisted of 17.5 µL of distilled water, 3 µL of HOT FIREPol® Probe Universal qPCR Mix (5× concentration), 1.5 µL of TaqMan® SNP Genotyping Assays (diluted 1:5), and 3 µL of genomic DNA.

The PCR conditions were: an initial 10-minute denaturation step at 95˚C, followed by 40 cycles: 15 seconds of denaturation at 95˚C, 1-minute hybridization/extension at 60˚C, and a concluding 30-second extension at 60˚C. The specific primers and probes employed for amplification are listed in Table 1.

Data were inputted into Excel 2019 and subsequently analyzed employing the Statistical Package for the Social Sciences (SPSS) version 20 and Stata version 16, in conjunction with EPI info 7.2.5.0. To ascertain risk levels, odds ratios (OR) along with their corresponding 95% confidence intervals (95% CI) were computed. A statistical difference was considering as significant when $p < 0.05$.

2.7. Ethical Considerations

The Ethics Committee for Health Research of Burkina Faso approved the protocol for this study under the reference N˚ 2022-02-027. All participants, including patients and donors, provided written informed consent prior to their inclusion in the study. Rigorous measures were adopted to maintain data confidentiality, with the database securely stored on a password-protected computer.

3. Results

3.1. Socio-Demographic Characteristics of the Study Population

- *MAP3K14* (rs2074292)

Table 1. Primer and probe sequences.

Polymorphism	Primers and probes
MAP3K14 (rs2074292)	Primers: F: 5'-AGCCCTGGAAACCTCACC-3' R: 5'-TGAGATTGGCGGAATAAGAGA-3' Probe: 5'-VIC-AGCCCTGGAAACCTCACC-MGB-NFQ-3' 5'-FAM-TGAGATTGGCGGAATAAGAGA-MGB-NFQ-3'
CD40 (rs1883832)	Primers: F: 5'-CCCCGATAGGTGGACCGCGATTGGT-3' R: 5'-CCCGCCCTCTGAACCCCCTACCAGT-3' Probe: 5'-VIC-CCCCGATAGGTGGACCGCGATTGGT-MGB-NFQ-3' 5'-FAM-CCCGCCCTCTGAACCCCCTACCAGT-MGB-NFQ-3'

Statistical Analysis.

The study population consisted of 223 participants with 109 (48.88%) women and 114 (51.12%) men. The sex ratio was 1.04. Population ages ranged from 12 to 80 years, with a mean study age of 34.84 ± 12.52 years. Females had a mean age of 34.51 ± 11.14 years, compared with 36.98 ± 13.26 years for males. Considering the clinical subgroups, the mean ages were as follows:

- Chronic hepatitis B (69 cases): 34.62 ± 11.86 years
- Cirrhosis (16 cases): 41.12 ± 11.81 years
- Hepatocellular carcinoma (48 cases): 42.10 ± 15.47 years
- Controls (90 persons): 30.03 ± 8.01 years of age

➢ *CD40* (rs1883832)

The study population comprised 173 individuals, 77 (44.5%) women and 96 (55.5%) men, with a sex ratio of 1.24. Their ages ranged from 12 to 80 years, with a mean of 35.88 ± 12.39 years. Females had a mean age of 34.51 ± 11.14 years, compared with 36.98 ± 13.26 years for males. Considering the clinical subgroups, the mean ages were as follows:

- Chronic hepatitis B (59 cases): 35 ± 11.07 years
- Cirrhosis (15 cases): 40.53 ± 11.10 years
- Hepatocellular carcinoma (46 cases): 41.85 ± 15.50 years
- Controls (53 persons): 30.36 ± 7.75 years

3.2. Genotypic and Allelic Frequencies of *MAP3K14* (rs2074292) and *CD40* (rs1883832) Stratified by Gender

➢ *MAP3K14* (rs2074292)

Females: In cases, genotype frequencies were 6.41% for wild-type AA homozygotes and GG-mutated homozygotes and 87.18% for AG heterozygotes. In controls, they were 8.33% for AA homozygotes, 87.5% for AG heterozygotes and 4.16% for GG mutated homozygotes. The mutated allele was represented in the case group with a frequency of 50% versus 47.9% in the control group. This difference was not statistically significant (p-value > 0.05).

Men: Genotype frequencies were 12.72% for AA homozygotes, 81.81% for AG heterozygotes and 5.45% for GG homozygotes in the case group. In controls, these values were 7.57% for AA homozygotes, 86.36% for AG heterozygotes and 6.06% for GG mutated homozygotes. The frequency of mutated alleles was 46.4% in cases versus 49.24% in controls, which did not represent a significant difference (p-value > 0.05) (**Table 2**).

➢ *CD40* (rs1883832)

Women: Genotype frequencies in cases were 60% for CC homozygotes, 10.8% for CT heterozygotes and 29.2% for TT mutated homozygotes. In controls, they were 41.7% for CC homozygotes, 8.3% for CT heterozygotes and 50% for TT mutated homozygotes. The frequency of the mutated allele was 34.6% in cases versus 54.2% in controls, with no significant difference (p-value > 0.05).

Men: In cases, the frequencies were 36.4% for CC homozygotes, 14.5% for CT heterozygotes and 49.1% for TT mutated homozygotes. In controls, 48.8% were CC homozygotes, 14.6% CT heterozygotes and 36.6% TT mutated homozygotes.

Table 2. Distribution of genotype and allele frequencies by sex.

		MAP3K14 (rs2074292)							
		Women				Men			
		Cases N = 78 (%)	Controls N = 24 (%)	OR (95% CI)	p-value	Cases N = 55 (%)	Controls N = 66 (%)	OR (95% CI)	p-value
Genotype	AA	5 (6.41)	2 (8.33)	Reference		7 (12.72)	5 (7.57)	Reference	
	AG	68 (87.18)	21 (87.5)	1.29 (0.23 - 7.17)	1	45 (81.81)	57 (86.36)	0.56 (0.16 - 1.89)	0.52
	GG	5 (6.41)	1 (4.16)	2 (0.13 - 29.80)	1	3 (5.45)	4 (6.06)	0.53 (0.08 - 3.53)	0.86
Alleles	A	78 (50)	25 (52.1)	Reference		59 (53.6)	67 (50.76)	Reference	
	G	78 (50)	23 (47.9)	1.08 (0.56 - 2.07)	0.93	51 (46.4)	65 (49.24)	0.89 (0.53 - 1.47)	0.75
		CD40 (rs1883832)							
		Women				Men			
		Cases N = 65 (%)	Controls N = 12 (%)	OR (95% CI)	p-value	Cases N = 55 (%)	Controls N = 41 (%)	OR (95% CI)	p-value
Genotypes	CC	39 (60)	5 (41.7)	Reference		20 (36.4)	20 (48.8)	Reference	
	CT	7 (10.8)	1 (8.3)	0.89 (0.09 - 8.8)	1	8 (14.5)	6 (14.6)	1.33 (0.39 - 4.54)	0.88
	TT	19 (29.2)	6 (50)	0.4 (0.1 - 1.5)	0.3	27 (49.1)	15 (36.6)	1.8 (0.74 - 4.35)	0.27
Alleles	C	85 (65.4)	11 (45.8)	Reference		48 (43.64)	46 (56.1)	Reference	
	T	45 (34.6)	13 (54.2)	0.44 (0.18 - 1.08)	0.11	62 (56.36)	36 (43.9)	1.65 (0.92 - 2.93)	0.11

The frequency of the mutated allele was 56.36% in cases versus 43.9% in controls, with no significant difference (p-value > 0.05) (Table 2).

As shown in Table 2, after distributing the frequencies of genotypes and alleles by sex, the analysis results indicated that there was no association between sex and the progression of infection with the hepatitis B virus towards severe forms of the disease at the level of the *MAP3K14* (rs2074292) and *CD40* (rs1883832) genes.

3.3. Distribution of Genotypic and Allelic Frequencies of *MAP3K14* (rs2074292) and *CD40* (rs1883832) Based on Clinical Status

To understand the potential relationship between the genotypic and allelic frequencies of polymorphisms in the *MAP3K14* (rs2074292) and *CD40* (rs1883832) genes and the progression of hepatitis B virus (HBV) infection, we examined

their distribution in the four clinical states: chronic hepatitis B (CHB), cirrhosis, HCC and controls. After analysis, the distribution of genotypes for the two polymorphic genes showed no specific trend or correlation related to any of the clinical groups. However, only the TT-mutated homozygote [OR = 0.05; 95% CI (0.01 - 1.16) and p < 0.00] and the T-mutated allele [OR = 0.17; 95% CI (1.1 - 0.29) and p < 0.00] of the rs1883832 polymorphism of the *CD40* gene offered protection against progression to severe forms of HBV infection (Table 3).

3.4. Comparison of Genotypic and Allelic Frequencies of *MAP3K14* (rs2074292) and *CD40* (rs1883832) Genes between Cases and Controls

- *MAP3K14* (rs2074292)

After analysis, there was no association between the rs2074292 polymorphism of the *MAP3K14* gene and the evolution of the infection. However, the mutated allele could be correlated with a low risk of infection severity (Table 4).

- *CD40* (rs1883832)

As shown in Table 4, for rs1883832 polymorphisms of the *CD40* gene, carriage of the mutated T allele has been shown to be associated with progression of hepatitis B virus infection to severe forms of the disease. This result applies to

Table 3. Genotype and allele frequencies by clinical status.

			General population N = 223 (%)	CHB N = 69 (%)	Cirrhosis N = 16 (%)	HCC N = 48 (%)	Controls N = 90 (%)	OR (95% CI)	p-Value
MAP3K14 (rs2074292)	Genotypes	AA	19 (8.52)	5 (7.24)	2 (12.5)	5 (10.41)	7 (7.77)	Reference	
		AG	191 (85.65)	61 (88.4)0	11 (68.75)	41 (85.41)	78 (86.66)	0.85 (0.32 - 2.24)	0.92
		GG	13 (5.82)	3 (4.34)	3 (18.75)	2 (4.16)	5 (55.55)	0.93 (0.21 - 3.99)	0.92
	Alleles	A	229 (51.35)	71 (51.45)	15 (46.87)	51 (53.13)	92 (51.1)	Reference	
		G	217 (48.65)	67 (48.55)	17 (53.13)	45 (46.87)	88 (48.9)	0.98 (0.67 - 1.43)	1
			General population N = 173 (%)	CHB N = 59 (%)	Cirrhosis N = 15 (%)	HCC N = 46 (%)	Controls N = 53 (%)	OR (95% CI)	p-Value
CD40 (rs1883832)	Genotypes	CC	118 (68.2)	57 (96.6)	8 (53.3)	28 (60.9)	25 (47.2)	Reference	
		CT	30 (17.3)	1 (1.7)	7 (46.7)	15 (32.6)	7 (13.2)	0.88 (0.34 - 2.29)	0.99
		TT	25 (14.5)	1 (1.7)	0	3 (6.5)	21 (39.6)	0.05 (0.01 - 1.16)	<0.001
	Alle les	C	266 (76.9)	115 (97.5)	23 (76.7)	71 (77.2)	57 (53.7)	Reference	
		T	80 (23.1)	3 (2.5)	7 (23.3)	21 (22.8)	49 (46.3)	0.17 (1.1 - 0.29)	<0.001

CHB: Chronic Hepatitis B; HCC: Hepatocellular Carcinoma; OR = Odds Ratio; CI = confidence interval; NA: Not applicable.

Table 4. Comparison of genotypic and allelic frequencies of CHB, cirrhosis, HCC and controls.

Genotypic and allelic frequencies in CHB and cirrhosis						
			CHB N = 69 (%)	Cirrhosis N = 16 (%)	OR (95% CI)	p-Value
MAP3K14 (rs2074292)	Genotypes	AA	5 (7.25)	2 (12.50)	Reference	
		AG	61 (88.41)	11 (68.75)	2.21 (0.38 - 12.90)	0.71
		GG	3 (4.35)	3 (18.75)	0.40 (0.04 - 3.95)	0.82
	Alleles	A	71 (51.45)	15 (46.87)	Reference	
		G	67 (48.55)	17 (53.13)	1.2 (0.5 - 2.59)	0.78
			CHB N = 59 (%)	Cirrhosis N = 15 (%)	OR (95% CI)	p-Value
CD40 (rs1883832)	Genotypes	CC	57 (96.6)	8 (53.3)	Reference	
		CT	1 (1.7)	7 (46.7)	49 (5.4 - 460.2)	<0.001
		TT	1 (1.7)	0	0 (NA)	1
	Alleles	C	115 (97.5)	23 (76.7)	Reference	
		T	3 (2.5)	7 (23.3)	11.66 (2.8 - 48.49)	<0.001
Genotypic and allelic frequencies in CHB and HCC						
			CHB N = 69 (%)	HCC N = 48 (%)	OR (95% CI)	p-Value
MAP3K14 (rs2074292)	Genotypes	AA	5 (7.25)	5 (10.42)	Reference	
		AG	61 (88.41)	41 (85.42)	1.48 (0.1 - 5.46)	0.79
		GG	3 (4.35)	2 (4.17)	1.5 (0.17 - 13.25)	1
	Alleles	A	71 (51.45)	51 (53.13)	Reference	
		G	67 (48.55)	45 (46.87)	0.93 (0.5 - 1.57)	0.9
			CHB N = 59 (%)	HCC N = 46 (%)	OR (95% CI)	p-Value
CD40 (rs1883832)	Genotypes	CC	57 (96.6)	28 (60.9)	Reference	
		CT	1 (1.7)	15 (32.6)	30.53 (3.83 - 243)	<0.001
		TT	1 (1.7)	3 (6.5)	6 (0.6 - 61.4)	0.23
	Alleles	C	115 (97.5)	71 (77.2)	Reference	
		T	3 (2.5)	21 (22.8)	11.33 (3.26 - 39.39)	< 0.001
Genotypic and allelic frequencies in CHB and Controls						
			CHB N = 69 (%)	Controls N = 90 (%)	OR (95% CI)	p-Value
MAP3K14 (rs2074292)	Genotypes	AA	5 (7.25)	7 (7.78)	Reference	
		AG	61 (88.41)	78 (86)	1.09 (0.33 - 3.61)	0.88
		GG	3 (4.35)	5 (5.56)	0.85 (0.3 - 5.26)	0.85
	Alleles	A	71 (51.45)	92 (51.1)	Reference	
		G	67 (48.55)	88 (48.9)	0.98 (0.63 - 1.53)	1

Continued

			CHB N = 59 (%)	Controls N = 53 (%)	OR (95% CI)	p-Value
CD40 (rs1883832)	Genotypes	CC	57 (96.6)	25 (47.2)	Reference	
		CT	1 (1.7)	7 (13.2)	0.06 (0.0073 - 0.53)	0.0046
		TT	1 (1.7)	21 (39.6)	0.02 (0.0027 - 0.16)	<0.001
	Alleles	C	115 (97.5)	57 (53.7)	Reference	
		T	3 (2.5)	49 (46.3)	0.03 (0.009 - 0.1)	<0.001

CHB: Chronic Hepatitis B; HCC: Hepatocellular Carcinoma; OR = Odds Ratio; CI = confidence interval; NA: Not applicable.

both homozygous and heterozygous carriers of the mutated allele. This allele would not only promote chronic infection by the virus, but also progression to cirrhosis and hepatocellular carcinoma, as shown by the ORs, CIs and p-values of the results obtained (Table 4).

3.5. Analysis of Combined Genotypes between Cases and Controls

To perform the combined genotype analysis for *MAP3K14* (rs2074292) and *CD40* (rs1883832) polymorphisms, we only considered samples that had passed SNP genotyping tests for both genes. The data in Table 5 show that simultaneous carriage of the above genotypes would increase the risk of progression from chronic HBV infection to cirrhosis or HCC (Table 5). Indeed, the combination of heterozygous AG genotypes of the *MAP3K14* gene (rs2074292) and CT genotypes of the *CD40* gene (rs1883832) was associated with a very high risk of progression of chronic hepatitis to cirrhosis (OR = 32; CI = 1.56 - 656.09; p = 0.045) or HCC (OR = 32; CI = 2.8 - 364.79; p = 0.004).

However, a protective effect against chronic infection was observed in cases of simultaneous carriage of the following genotypes:

- *MAP3K14* genotype AG (rs2074292) and *CD40* genotype CT (rs1883832)
- *MAP3K14* genotype AG (rs2074292) and *CD40* genotype TT (rs1883832)

The results of the combined effects showed a trend according to which subjects carrying risk genotypes (rs2074292 AG and rs1883832 CT, TT), could be linked to a protective effect (p < 0.001).

3.6. Comparison of Genotypic and Allelic Frequencies of *MAP3K14* (rs2074292) and *CD40* (rs1883832) Genes between Cirrhosis, HCC and Controls

For the *MAP3K14* (rs2074292) and *CD40* (rs1883832) polymorphisms, no significant association was identified between the different genotypes and progression from cirrhosis to HCC.

Compared with the progression of infection in the cirrhosis and control groups, the homozygous TT mutated genotype and the T mutated allele confer protection against the progression of infection to cirrhosis [OR = 0.35; 95% CI (0.13 - 0.89) and p-value = 0.04].

Table 5. Combined genotypes between CHB, cirrhosis, HCC and controls.

	MAP3K14 (rs2074292)												
	AA				AG				GG				
CD40 (rs1883832)	CHB	Cirrhosis	OR (95% CI)	p-Value	CHB	Cirrhosis	OR (95% CI)	p-Value	CHB	Cirrhosis	OR (95% CI)	p-Value	
CC	8	1	**Reference**		45	5	0.88 (0.09 - 8.64)	1	4	2	1 (0.27 - 58.56)	0.69	
CT	0	1	NA	0.42	1	4	32 (1.56 - 656.09)	**0.045**	0	1	NA	0.42	
TT	0	0	NA	NA	1	0	NA	1	0	0	NA	NA	
	MAP3K14 (rs2074292)												
	AA				AG				GG				
CD40 (rs1883832)	CHB	HCC	OR (95% CI)	p-Value	CHB	HCC	OR (95% CI)	p-Value	CHB	HCC	OR (95% CI)	p-Value	
CC	8	3	**Reference**		45	23	1.36 (0.32 - 5.63)	0.93	4	1	0.66 (0.05 - 8.63)	1	
CT	0	2	NA	0.24	1	12	32 (2.8 - 364.79)	**0.004**	0	1	NA	0.71	
TT	0	0	NA	NA	1	3	8 (0.58 - 110.27)	0.28	0	0	NA	NA	
	MAP3K14 (rs2074292)												
	AA				AG				GG				
CD40 (rs1883832)	CHB	Controls	OR (95% CI)	p-Value	CHB	Controls	OR (95% CI)	p-Value	CHB	Controls	OR (95% CI)	p-Value	
CC	8	1	**Reference**		45	20	0.28 (0.03 - 2.4)	0.4	4	1	0.5 (0.02 - 10.25)	1	
CT	0	0	NA	NA	1	5	0.02 (0.0013 - 0.49)	**0.02**	0	0	NA	NA	
TT	0	2	NA	0.09	1	18	0.0069 (0.00004 - 0.12)	**0.00006**	0	1	NA	0.42	

Also, the homozygous TT mutated genotype and T mutated allele the *CD40* (rs1883832) were associated with protection against the development of carcinoma in HBV infection [OR = 0.12; 95% CI (0.03 - 0.47) and p-value = 0.0019], [OR = 0.34; 95% CI (0.18 - 0.63) and p-value = 0.001] respectively (Table 6).

3.7. Combined Genotype Analysis between Cirrhosis, HCC and Controls

For progression from cirrhosis to carcinoma, analysis of the combined genotypes of the two polymorphisms showed no association between controls compared to patients with cirrhosis, nor between patients with cirrhosis and those with HCC.

Table 6. Comparison of genotypic and allelic frequencies of cirrhosis, HCC and controls.

Genotypic and allelic frequencies in cirrhosis and HCC						
			Cirrhosis N = 16 (%)	HCC N = 48 (%)	OR (95% CI)	p-Value
MAP3K14 (rs2074292)	Genotypes	AA	2 (12.5)	5 (10.41)	Reference	
		AG	11 (68.75)	41 (85.41)	1.49 (0.25 - 8.75)	1
		GG	3 (18.75)	2 (4.16)	0.26 (0.02 - 3.02)	0.62
	Alleles	A	15 (46.87)	51 (53.13)	Reference	
		G	17 (53.13)	45 (46.87)	0.77 (0.34 - 1.73)	0.68
			Cirrhosis N = 15 (%)	HCC N = 46 (%)	OR (95% CI)	p-Value
CD40 (rs1883832)	Genotypes	CC	8 (53.3)	28 (60.9)	Reference	
		CT	7 (46.7)	15 (32.6)	0.61 (0.18 - 2.01)	0.61
		TT	0	3 (6.5)	NA	0.86
	Alleles	C	23 (76.7)	71 (77.2)	Reference	
		T	7 (23.3)	21 (22.8)	0.97 (0.36 - 2.57)	1
Genotypic and allelic frequencies in cirrhosis and controls						
			Cirrhosis N = 16 (%)	Controls N = 90 (%)	OR (95% CI)	p-Value
MAP3K14 (rs2074292)	Genotypes	AA	2 (12.5)	7 (7.77)	Reference	
		AG	11 (68.75)	78 (86.66)	0.49 (0.09 - 2.68)	0.75
		GG	3 (18.75)	5 (55.55)	2.1 (0.25 - 17.59)	0.87
	Alleles	A	15 (46.87)	92 (51.1)	Reference	
		G	17 (53.13)	88 (48.9)	1.18 (0.55 - 2.51)	0.8
			Cirrhosis N = 15 (%)	Controls N = 53 (%)	OR (95% CI)	p-Value
CD40 (rs1883832)	Genotypes	CC	8 (53.3)	25 (47.2)	Reference	
		CT	7 (46.7)	7 (13.2)	3.12 (0.83 - 11.64)	0.16
		TT	0	21 (39.6)	0 (NA)	0.04
	Alleles	C	23 (76.7)	57 (53.7)	Reference	
		T	7 (23.3)	49 (46.3)	0.35 (0.13 - 0.89)	0.04
Genotypic and allelic frequencies in HCC and Controls						
			HCC N = 48 (%)	Controls N = 90 (%)	OR (95% CI)	p-Value
MAP3K14 (rs2074292)	Genotypes	AA	5 (10.41)	7 (7.77)	Reference	
		AG	41 (85.41)	78 (86.66)	0.73 (0.21 - 2.46)	0.85
		GG	2 (4.16)	5 (55.55)	0.56 (0.07 - 4.14)	0.93
	Alleles	A	51 (53.13)	92 (51.1)	Reference	
		G	45 (46.87)	88 (48.9)	0.92 (0.56 - 1.51)	0.84

Continued

			HCC N = 46 (%)	Controls N = 53 (%)	OR (95% CI)	p-Value
CD40 (rs1883832)	Genotypes	CC	28 (60.9)	25 (47.2)	Reference	
		CT	15 (32.6)	7 (13.2)	1.91 (0.67 - 5.44)	0.33
		TT	3 (6.5)	21 (39.6)	0.12 (0.03 - 0.47)	0.0019
	Alleles	C	71 (77.2)	57 (53.7)	Reference	
		T	21 (22.8)	49 (46.3)	0.34 (0.18 - 0.63)	0.001

CHB: Chronic Hepatitis B; HCC: Hepatocellular Carcinoma; OR = Odds Ratio; CI = confidence interval; NA: Not applicable.

In contrast, simultaneous carriage of the homozygous TT mutated genotype of *CD40* (rs1883832) and the GA of *MAP3K14* (rs20742) [OR = 0.05; 95% CI (0.004 - 0.7) and p-value = 0.049] had a protective effect against the development of HCC (Table 7).

4. Discussion

The aim of this study was to investigate the involvement of *MAP3K14* rs2074292 and *CD40* (rs1883832) genes polymorphisms in the evolution of hepatitis B virus infection in Burkina Faso.

Analysis of data by socio-demographic characteristics showed that the mean age of our study population was 35.31 ± 11.96 years for *MAP3K14* (rs2074292) and 34.51 ± 11.14 years for *CD40* (rs1883832). The average age of cases was higher than that of controls (42.10 ± 15.47 years for HCC vs 30.03 ± 8.01 years for controls). Our results corroborate those of SOME *et al.* who argue that in sub-Saharan Africa, HCC is most often diagnosed in patients in the 40 - 50 age range [16]. Our results are close to those of previous studies carried out at the Yalgado OUEDRAOGO teaching Hospital Center, which found average ages for cirrhosis patients of 46.5 years and 46.9 years in 2002 and 2020 respectively [16] [17]. However, our results differ from those of a study carried out in America, where the average age was around 60 years [18]. The results showed that our patients were younger than those in developed countries, which could be due to the high proportion of young people in Burkina Faso. This could be explained by the fact that HBV prevalence is high in sub-Saharan Africa, and access to the healthcare system is limited compared with other regions of the world.

Analysis *MAP3K14* (rs2074292) gene polymorphism data in the general study population shows that, the frequencies of the AA, AG and GG genotypes were 8.52%, 85.65% and 5.82% respectively. For allelic distribution, the wild-type A allele had a frequency of 51.35% versus 48.65% for the mutated allele. Our results differ to those of Huang *et al.* in China, who found 21.59% for AA genotype; 51.62% for AG genotype and 27.25% GG even if our both results show a predominance heterozygote AG [11]. Our allelic frequencies also differ to those

Table 7. Combined genotypes between cirrhosis, HCC and controls.

	MAP3K14 (rs2074292)											
	AA				AG				GG			
CD40 (rs1883832)	Cirrhosis	HCC	OR (95% CI)	p-Value	Cirrhosis	HCC	OR (95% CI)	p-Value	Cirrhosis	HCC	OR (95% CI)	p-Value
CC	1	3	**Reference**		5	23	1.5 (0.13 - 17.9)	1	2	1	0.16 (0.006 - 4.5)	1
CT	1	2	0.66 (0.02 - 18)	1	4	12	1 (0.07 - 12.5)	1	1	1	0.33 (0.009 - 11.9)	0.7
TT	0	0	NA	NA	0	3	NA	1	0	0	NA	NA
	MAP3K14 (rs2074292)											
	AA				AG				GG			
CD40 (rs1883832)	Cirrhosis	Controls	OR (95% CI)	p-Value	Cirrhosis	Controls	OR (95% CI)	p-Value	Cirrhosis	Controls	OR (95% CI)	p-Value
CC	1	1	**Reference**		5	20	0.25 (0.01 - 4.7)	0.9	2	1	2 (0.05 - 18.25)	1
CT	1	0	NA	1	4	5	0.8 (0.03 - 17.19)	1	1	0	NA	1
TT	0	2	NA	1	0	18	NA	0.17	0	1	NA	1
	MAP3K14 (rs2074292)											
	AA				AG				GG			
CD40 (rs1883832)	HCC	Controls	OR (95% CI)	p-Value	HCC	Controls	OR (95% CI)	p-Value	HCC	Controls	OR (95% CI)	p-Value
CC	3	1	**Reference**		23	20	0.38 (0.03 - 3.9)	0.7	1	1	0.33 (0.009 - 11.9)	1
CT	2	0	NA	1	12	5	0.8 (0.06 - 9.6)	1	1	0	NA	1
TT	0	2	NA	0.38	3	18	0.05 (0.004 - 0.7)	**0.049**	0	1	NA	0.8

of Huang who obtain 53.06% for G allele and 46.94% A allele. The difference in genotype and allele frequencies in our study could be explained by the genotype of the two study populations, black versus Chinese.

We correlated *MAP3K14* gene polymorphisms with different stages of HBV infection and found no significant association. These results differ from those of Hung, who showed that the AA and AG genotypes were associated with a high risk of complications of HBV infection, notably HCC [11]. Nevertheless, our results showed that the GG mutated genotype is associated with protection against severe forms of HBV infection, although this result was not significant enough.

Analysis of polymorphism data for the *CD40* gene (rs1883832) in the general population studied showed that the frequencies of the CC, CT and TT genotypes

were 68.2%, 17.3% and 14.5% respectively. In terms of allelic distribution, the wild-type C allele had a frequency of 76.9%, compared with 23.1% for the mutated T allele. These genotypic frequencies differ from those of Tian *et al.* 2019, who found 38.6%, 47% and 14.4% for the CC, CT and TT genotypes, respectively. [19].

Our allele frequencies also differ from those of Tian *et al.* who obtained 62.1% for the C allele and 37.9% for the T allele. The difference in genotype and allele frequencies in our two studies could be explained by the genotype of the two populations studied, black versus Chinese. [19].

There was an association between *CD40* gene polymorphisms and different stages of HBV infection. Indeed, the mutated T allele and the heterozygous CT genotypes of rs1883832 T were associated with the progression of HBV infection towards severe forms of the disease, notably between chronic carriers and those with cirrhosis and HCC. The mutated allele would favor not only chronic infection with the virus, but also progression to cirrhosis and hepatocellular carcinoma, as shown by the ORs, CIs and p-values of the results obtained. These results correspond with those found by Jia Xuan Chen et al who demonstrated in a similar study that the SNP rs1883832 located in the 5'UTR of *CD40* was involved in the risk of CHB, the rs1883832 T allele representing the risk, while the C allele is protective [20]. One possible explanation is that the presence of the T allele within the *CD40* gene could affect gene translation by influencing mRNA-ribosome stability and the function of cytokines and T cells. [21].

In addition, the homozygous mutated TT genotype and the mutated allele of the *CD40* gene (rs1883832) were associated with protection against the development of cirrhosis and carcinoma in HBV infection.

However, our results differ from those of Tain *et al.*, who associated the homozygous mutated genotype with a low risk of developing severe forms of the disease. [19].

Analysis of the combined genotypes of the 2 polymorphisms revealed a significant association between the two heterozygous genotypes CT of rs1883832 and AG of rs2074292. Indeed, the combination of these genotypes could be associated with an elevated risk of progression from chronic infection to cirrhosis or HCC.

In contrast, the AG heterozygote of rs2074292*MAP3K14* combined with the CT heterozygote and TT mutated homozygote genotypes of rs1883832*CD40* was associated with protection against chronic hepatitis. Our study also demonstrated protection against HCC conferred by the combination of the TT-mutated homozygous genotype of *CD40* (rs1883832) and the AG heterozygote of *MAP3K14* (rs2074292).

5. Conclusions

Our study was the first to investigate the association between *CD40* (rs1883832) and *MAP3K14* (rs2074292) polymorphisms and the occurrence of severe forms of HBV infection in the population from Burkina Faso. This study showed that

the heterozygous CT genotype and the mutated T allele of the *CD40* gene (rs1883832) are involved in the progression of chronic hepatitis to cirrhosis and hepatocellular carcinoma in HBV-infected patients. Thus, this study showed that *CD40* SNP rs1883832 has its unique mechanism of modulating HBV clearance in hepatocytes. However, no association was found between polymorphisms in the *MAP3K14* gene (rs2074292) and the progression of HBV infection. By combining the two polymorphisms, we found associations that conferred protection against chronic hepatitis and HCC, and elevated risks of progression from chronic infection to cirrhosis and HCC.

It is possible that an interaction between several factors may better explain the emergence of severe forms of HBV infection in Burkina Faso, in order to better understand the different pathways and factors that contribute to these associations. Further research in this area is therefore needed, and could help to improve the prevention, diagnosis and treatment of HBV infection, particularly in high-prevalence regions such as Burkina Faso.

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Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee for Health Research (reference: deliberation N˚ 2022-02-027). Written informed consent was obtained from patients and donors. We ensured the confidentiality of our database by storing it on a password-protected computer.

Consent for Publication

Not Applicable.

Availability of Data and Materials

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

Conflicts of Interest

The authors declare that they have no competing interests.

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Authors' Contributions

Study concept and design: LT, SVZ, FWD and JS. Sampling and laboratory analysis: LT, NN, SK, ARK, MNT, SVZ, MST and TRC. Statistical analysis and

data interpretation: LT, NN, SK, MNT and AKO. Drafting of the manuscript: LT, NN, SK and AKO. Critical revision of the manuscript for important intellectual content: SVZ, AKO, MS, MST, BD, DPI, TS, ATY, BMN, FWD and JS. Administrative, technical and material support: LT, BMN, ATY, FWD and JS. Study supervision: BLN, ATY, FWD and JS. The corresponding author declares that the manuscript has been read and approved by all named authors and that the order of authorship in the manuscript has been approved by all of us.

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List of Abbreviations

ALAT: Alanine Amino Transferase
CHB: Chronic Hepatitis B
DNA: Deoxyribonucleic Acid
CD40: Cluster of Differentiation 40
MAP3K14: Mitogen-Activated Protein Kinase Kinase Kinase 14
HBsAg: HBs Antigen
HBV: Hepatitis B Virus
HCC: Hepatocellular Carcinoma
HCV: Hepatitis C Virus
HIV: Human Immunodeficiency Virus
HLA: Human Leukocyte Antigen
NF-κB: nuclear Factor-Kappa B
WHO: World Health Organization
Rs: Reference of SNP
SNP: Single Nucleotide Polymorphism