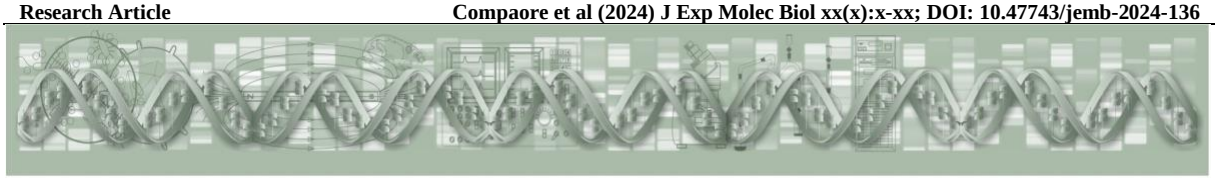

LINKAGE BETWEEN ACE2 GENE POLYMORPHISMS AND SARS-COV-2 INFECTION IN BURKINA FASO, SUB-SAHARAN AFRICA

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Abstract

The *ACE2* gene polymorphisms (rs143936283, rs146676783, and rs4646116) in infected and noninfected persons by SARS-CoV-2 in Burkina Faso. Our cross-sectional study population comprised 137 SARS-CoV-2 infected persons and 181 non-infected persons. Three *ACE2* gene polymorphisms, rs143936283, rs146676783, and rs4646116, were genotyped using the real-time PCR standard TaqMan allelic discrimination technique. The association between SARS-CoV-2 infection and the polymorphisms were evaluated by a binary logistic regression. There was no association between the polymorphisms rs143936283 rs4646116 haplotypes, and SARS-CoV-2 infection in our study population. However, in the female population, the heterozygous genotype CT of rs146676783 increased by two and half the risk (OR=2.58 95%CI (1.2-5.48), p= 0.014) of being infected by SARS-CoV-2. Additionally, carrying the homozygous minor allele (genotype TT) of rs146676783 increased by more than five and half the risk (OR=5.57 95%CI (1.64-18.78), p=0.006) of being infected by SARS-CoV-2 among females. This study showed that the *ACE2* gene variant rs146676783 was associated with an increased risk of being infected by SARS-CoV-2 in females, suggesting a need for further investigation to contribute to a better understanding of the African COVID-19 enigma**.**
Keys words: SARS-CoV-2, ACE2, polymorphism, haplotypes, Burkina Faso

Introduction

The corona disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has severely challenged the global health system worldwide. Africa and particularly Burkina Faso, was not an exception (Abdou Azaque Zoure

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2022). In Burkina Faso, the first case of COVID-19 was recorded early March 2020 (Ouattara et al. 2023; Savadogo M 2021). High seroprevalence of SARS-CoV-2 was recorded in Burkina Faso but mainly in asymptomatic patients, as shown by the studies of(Sagna et al. 2022; Struck et al. 2022) compared to Western countries with higher symptomatic cases and higher deaths. This discrepancy could be due to genetic and environmental factors. The genetic elements implied in SARS-CoV-2 infections are ACE2, cellular transmembrane serine protease two (TMPRSS2), and endosomal/lysosomal cysteine proteases cathepsin B and L (CTSB) (Trougakos et al. 2021).

Studies have shown that the *angiotensin-converting enzyme 2 (ACE2*) gene is on the X-chromosome (Srivastava et al. 2020; Zhou et al. 2020). The main entry of the virus into human cells is through the angiotensin-converting enzyme (ACE) receptor two, which exists in two (2) forms, a full-length m*ACE2*, and a s*ACE2*, a soluble form found in circulation (Nelson-Sathi et al. 2022; Scialo et al. 2020). The spike (s) protein on the SARS-CoV-2 envelope *ACE2* found on human cell membranes, consisting of a transmembrane anchor and an extracellular domain. The protein S of SARS-CoV-2 is cleaved into S1 and S2, and the interaction of the complex S1 protein/receptor is crucial for the virus to infect a host cell (Batlle et al. 2020; Samavati and Uhal 2020). The severity of the COVID-19 disease could be alleviated by a decreased level of *ACE2*. Moreover, cardiovascular homeostasis and electrolyte balance, as well as lung injury protection, are sustained by ACE2 (Yang et al. 2020). *ACE2* gene variants have been shown to have a functional role in binding the SARS-CoV-2 spike protein (Cruz et al. 2021; Hussain et al. 2020). Of which rs143936283 and rs4646116, two of the missense single nucleotide variation (SNV) have a higher susceptibility to SARS-CoV-2 infection (Hussain et al. 2020). The SNV rs4646116 had a population allele frequency (AF) of 0.012 in Ashkenazi Jewish, 0.005 in European, 0.0033 in American, and 0.0008 in Asian populations based on the Genome Aggregation Database (gnomAD) (Suryamohan et al. 2021). The SNV rs146676783 is one of the missense SNVs whose allele frequency is 0.0001 in European and African people based on the Gnom AD exomes data and is thought to lessen SARS-CoV-2 infection susceptibility (Wang et al. 2020). African countries such as Burkina Faso have had low hospitalized and death related to COVID-19 ((JHU) 2023; JHU 2023).Furthermore, data on *ACE2* gene polymorphism associated with SARS-Cov-2 infection in Africa is scarce. Our study aimed to evaluate the *ACE2* gene single nucleotide polymorphisms (SNPs), rs143936283, rs146676783, and rs4646116 among infected or noninfected persons by SARS-CoV-2 in Burkina Faso.

Material and Methods

Study subjects

It was a cross-sectional study between August and November 2022 in Ouagadougou, the capital of Burkina Faso. The study included 137 positive and 181 negative cases. The positive and negatives cases were tested by real-time PCR using the Quant Studio 5 (Applied Biosystems). All samples were tested for antibodies against SARS-CoV2 by ELISA using the WANTAI SARS-CoV-2 Ab ELISA kit (Wantai SARS-CoV-2 Diagnostics). This study included nasal or oropharyngeal and blood samples collected from non-vaccinated persons between November 2020 and December 2021 from the Biomedical Research laboratory of the "Institut de Recherche en Sciences de la Sante) and the Pietro Annigoni Biomolecular Research Center (CERBA).

Screening and genotyping of the selected Single Nucleotide Polymorphisms (SNPs)

According to the manufacturer's protocol, the "PureLink™ Genomic DNA" mini kit (Invitrogen) was used to extract genomic DNA from the nasopharyngeal swabs. The SNP were selected from the PubMed database literature and presented in Table 1. The genotyping of the selected polymorphism of the *ACE2* gene was performed by the standard allelic

discrimination technique using TaqMan® probes based on the 5'exonuclease activity of DNA polymerase by real-time PCR on Quantstudio 5 (Applied Biosystems). The amplification program was as follows a pre-amplification step at 60 °C for 30 seconds, denaturation at 95 °C for 10 minutes followed by 40 hybridization cycles at 95 °C for 15 seconds, 40 elongation cycles at 60 °C for 1 minute, and a final elongation of 60 °C for 30 seconds.
The Haploview software 4.1 ensured that our selected SNPs (rs143936283, rs146676783, and rs4646116) minor allele frequencies were ≥ 1.

Ethical Considerations

The protocol approval for the study was obtained from the Ethics Committee for Health Research in Burkina Faso (number 2022-02-035). The patients' samples were handled with anonymity by using a codification system.

Data Processing and Analysis

Data were entered using Excel 2016 software. These data were then analyzed using Statistical Package for Social Sciences (SPSS) version 25.0.0.0. Frequencies were used to classify variables. The chi-square test was used to compare the difference between the distributions. Since the *ACE2* gene is located on chromosome X, the distribution of the selected SNPs is presented as positive and negative SARS-CoV-2 groups stratified by gender. Binary logistic regression tests were then determined by adjusting the odds ratio (OR) with age. We also analyzed overdominant, dominant, and recessive models to evaluate the inheritance model. Haplotype analysis was done using Haploview 4.1 software. The difference was statistically significant for $p \leq 0.05$.

Tabe 1: Marker information

Gene	SNP rs#	Position	Database Alleles	Reference Allele	Amino Acid change
Ace2, Chr X	rs143936283	15581305	T>C	T	E329G
	rs146676783	15600803	C>T	C	E37K
	rs4646116	15600835	T>C	T	K26R

RESULTS

Study population

Samples from 137 individuals infected with SARS-CoV-2 and 181 not infected were successfully genotyped.
The mean age of our study population was 34.30 ± 14.93 years. Male participants were more represented than females, with a sex ratio (M/F) of 1.10. The age group of 25-40 years was the most represented in both SARS-CoV-2-infected and uninfected groups. Furthermore, age seems to be linked to SARS-CoV-2 infection status $p=0.051$ (Table 2).

Table 2. Socio-demographic data

Characteristics	Negative cases n (%)	Positive cases n (%)	*p-value*
Sex			
Female	88 (48.6)	63 (46)	*0.652*
Male	93 (51.4)	74 (54)	
Total	181 (56.9)	137 (43.1)	
Age group (years)			
<24	50 (27.6)	31 (22.6)	
25-40	79 (43.6)	66 (48.2)	*0.051*
41-55	36 (19.9)	17 (12.4)	

55>	16 (8.8)	23 (16.8)
Total	181 (59.1)	137 (40.9)

Association between Age by sex and SARS-CoV-2 infection status

Table 3 shows that age groups among women are not related to the SARS-CoV-2 infection status. Among males, subjects aged over 55 had three (3) an increased risk compared to patients younger than 24 but it was not statistically significant [OR=3.08 ; 95%CI (0.925-10.25); *p*=0.067].

Table 3: *Association between Age, sex, and SARS-CoV-2 infection status*

Age groups	Negative n (%)	Positive n (%)	OR	95% CI	p-value
Female					
<24	22 (25)	11 (17.5)		**Reference**	
25-40	38 (43.2)	29 (46)	1.526	0.64-3.64	0.34
41-55	17 (19.3)	11 (17.5)	1.294	0.45-3.69	0.63
55>	11 (12.5)	12 (19)	2.18	0.73-6.5	0.16
Male					
<24	28 (30)	20 (27)		**Reference**	
25-40	41 (44.1)	37 (50)	1.263	0.61-2.61	0.53
41-55	19 (20.4)	6 (8.1)	0.442	0.15-1.30	0.14
55>	5 (5.4)	11 (14.9)	3.08	0.925-10.25	0.067

OR: odds ratio, **CI:** confidence interval

Comparison of ACE2 gene polymorphism between cases and controls

The polymorphism rs143936283 and rs4646116 have both TT as the normal homozygous genotype and TC as the heterozygous genotype, while rs146676783 have CC as the normal homozygous genotype and CT has the heterozygous genotypes.

The overall minor allele frequency (MAF) of rs143936283 was C = 0.311, the MAF of rs146676783 was T = 0.307, and that of rs4646116 was C = 0.247 in our study population n. Table 4 displayed the allele frequency distribution of these three single nucleotide polymorphisms of the *ACE2* gene in cases and control groups. It also shows clearly that one (1) polymorphism, rs146676783, is related to the infection SARS-CoV-2

Table 4. Allele frequency of *ACE2* gene polymorphism between SARS-CoV-2 infected and noninfected in a population from Burkina Faso

SNPs	Negative n (%)	Positive n (%)	n (%)	χ^2	*p-value*
		rs143936283			
T	231 (63.8)	184 (67.2)	415 (65.3)	0.768	*0.381*
C	131 (36.2)	90 (32.8)	221 (34.7)		
		rs146676783			
C	277 (76.5)	177 (64.60)	454 (71.4)	10.85	***0.001***
T	85 (23.5)	97 (35.40)	182 (28.6)		

		rs4646116			
T	299 (82.6)	236 (86.1)	535 (84.1)	1.459	*0.227*
C	63 (17.4)	38 (13.9)	101 (15.9)		

Association between ACE2 gene polymorphisms and infection by SARS-CoV-2 in male patients

Table 5 shows that in terms of allele frequencies of each *ACE2* SNP studied, and there is no statistical difference between the two groups. Furthermore, genotypically-wise, there was also no statistical significance for SARS-CoV-2 infection. As shown in Table 2, age is a factor that might be related to SARS-CoV-2 disease among males. The association between *ACE2* gene polymorphism and SARS-CoV-2 infection odds ratio was adjusted for age to avoid its influence, and there was no statistical significance.

Table 5. Allelic frequency and association of *ACE2* gene polymorphisms and infection by SARS-CoV-2 in male patients

SNPs	**Negative, n (%)**	**Positive, n (%)**	**OR (95% CI)**	***p-value***
		rs143936283		
T	138 (74.2)	108 (73.0)	**Reference**	-
C	48 (25.8)	40 (27.0)	1.065 (0.683 – 1.737)	*0.801*
		rs146676783		
C	144 (77.4)	108 (73.0)	**Reference**	-
T	42 (22.6)	40 (27.0)	1.270 (0.770 – 2.093)	*0.349*
		rs4646116		
T	168 (90.3)	140 (94.6)	**Reference**	-
C	18 (9.7)	8 (5.4)	.833 (0.225-1.264)	*0.153*

Association between ACE2 gene polymorphisms and infection by SARS-CoV-2 in female patients

The genotypic distributions of rs146676783 and rs4646116 were consistent with the Hardy-Weinberg equilibrium law, and the *p-values* were 0.978 and 0.457, while rs143936283 was not consistent with the *p-value* was 0.027. When comparing the case and control groups in female for the 3 SNPs in Table 6, the minor Allele T of rs146676783 seem to increase by more than two (2) times the risk of being infected by SARS-CoV-2 among females, and it was statistically significant (*p <0.001*). Regarding genotyping frequency, when the odds ratio was adjusted for age, the CT of rs146676783 increased by two and half the risk of being infected by SARS-CoV-2 [OR=2.582; 95%CI (1.216-5.485); *p=0.014*]. Additionally, genotype TT of rs146676783 increased by almost more than five and half times the risk of being infected by SARS-CoV-2 among females [OR=5.557; 95%CI (1.644-18.785); *p=0.006*].

Table 6: Genotype and allele frequencies of three genetic polymorphisms among negative patients and SARS-CoV-2 infected female patients

Genotype	**Negative, n (%)**	**Positive, n (%)**	**OR (95% CI)**	***p-value***
		rs143936283		
TT	20 (22.7)	20 (31.7)	**Reference**	-
TC	53 (60.2)	36 (57.1)	0.658 (0.203-2.132)	*0.485*

CC	15 (17.0)	7 (11.1)	0.883 (0.391-1.995)	*0.765*
C	83 (47.2)	50 (39.7)	0.737 (0.464-1.172)	*0.197*
		rs146676783		
CC	50 (56.8)	18 (28.6)	**Reference**	-
CT	33 (37.5)	33 (52.4)	**2.582 (1.216-5.485)**	***0.014***
TT	5 (5.7)	12 (19.0)	**5.557 (1.644-18.785)**	***0.006***
T	43 (24.4)	57 (45.2)	**2.55 (1.56-4.176)**	***< 0.001***
		rs4646116		
TT	49 (55.7)	34 (54.0)	**Reference**	-
TC	33 (37.5)	28 (44.4)	1.166 (.564-2.410)	*0.678*
CC	6 (6.8)	1(1.6)	0.356 (.039-3.219)	*0.358*
C	45 (25.6)	30 (23.8)	0.91 (.535-1.548)	*0.727*

TT: *Homozygous genotype of* ***T*** *alleles;* ***CT :*** *Heterozygous genotype of* ***C*** *and* ***T*** *alleles,* ***TC:*** *Heterozygous genotype of* ***T*** *and* ***C*** *alleles.****OR:*** *odds ratio,* ***CI****: confidence interval*

We then analyzed the risk of association between female patients' genotype and SARS-CoV-2 infection by looking at the over-dominant, dominant, and recessive inheritance models (Table 7). The odds ratio shows statistical differences for the dominant [OR=3.289; 95%CI (1.649-6.561); *p=0.001*] and recessive [OR=3.906; 95%CI (1.300-11.734); *p=0.015*] models for rs146676783.

Table 7: Association between 3 single loci and SARS-CoV-2 infection Status, Based on Overdominant, Dominant, and Recessive Models

Markers	Models	OR	95% CI	*p-Value*
rs143936283	TT&CC (referent) vs TC, Overdominant	0.881	0.457-1.698	*0.704*
	TT*vs*.TC &CC, Dominant	0.632	0.305-1.31	*0.217*
	CC *vs*. TT &TC, Recessive	0.608	0.232-1.693	*0.311*
rs146676783	CC&TT (referent) vs CT, Overdominant	1.833	0.951-3.534	*0.07*
	CC *vs*. CT & TT, Dominant	**3.289**	**1.649-6.561**	***0.001***
	CC & CT *vs*. TT Recessive	**3.906**	**1.300-11.734**	***0.015***
rs4646116	TT&CC (referent) vs TC Overdominant	1.333	0.690-2.575	*0.392*
	TT *vs*. TC & CC, Dominant	1.072	0.560-2.053	*0.835*
	TT & TC *vs* CC, Recessive	0.220	0.026-1.878	*0.167*

TT: *Homozygous genotype of* ***T*** *alleles;* ***CT:*** *Heterozygous genotype of* ***C*** *and* ***T*** *alleles,* ***TC:*** *Heterozygous genotype of* ***T*** *and* ***C*** *alleles.****OR:*** *odds ratio,* ***CI****: confidence interval*

Linkage Disequilibrium and Haplotype Analysis

As the three (3) SNVs are on chromosome X, linkage disequilibrium and haplotype analysis were carried out; results are shown in the supplementary file, implying that rs143936283 and rs146676783 might fall in the same linkage area in male subjects. The 3 SNPs were in linkage disequilibrium. The haplotype analysis displayed that rs143936283 and rs146676783 of the *ACE2* gene define a block of 19 Kb. Furthermore, three (3) sorts of haplotype (combination frequency >5%) are yielded from this analysis, among which the "T-C" had the higher frequency, 67.7%, followed by "T-T" (24.6%) and "C-C" (7.8%) in male patients. There was no association between SARS-CoV-2 infection and *ACE2* gene SNP haplotypes in males. The haplotype analysis was also conducted in the female population and did not yield a haplotype.

Discussion

To our knowledge, this is one of the first studies addressing the association of *ACE2* gene polymorphisms (rs143936283, rs146676783, and rs4646116) with SARS-CoV-2 infection. The mean age of our study population was 34.30 ± 14.93 years, which is coherent with the other studies carried out in Burkina Faso (Compaore et al. 2016) but different from the mean age in studies from China which were between 49 and 55 years (Abdou Azaque Zoure 2022). This difference could be due to the critical youth proportion in Burkina Faso (INSD 2022). Our study results show that age seems to be a risk factor for SARS-CoV-2 infection, especially among males. Age-wise, our study showed that males over 55 years had three (3) times an increased risk of being infected by SARS-CoV-2 compared to those who were younger than 24 years. This observation is consistent with the literature showing that older people are more likely to be infected by SARS-CoV-2 (Farshbafnadi et al. 2021).

ACE2 expression in plasma is linked to SARS-CoV-2 infection (Scialo et al. 2020). However, we could not carry out that experiment, but we concentrated on three single nucleotide variations (rs143936283, rs146676783, and rs4646116). The minor allele frequencies of these SNP in our population differed from those of western or Asian descent (Darbani 2020). Our study shows that *ACE2* gene polymorphism rs146676783 is linked with SARS-CoV-2 infection, and it was statistically significant with $p=0.001$. To further understand the link between *ACE2* gene rs143936283, rs146676783, and rs4646116, we stratified the alleles and genotype frequencies by gender. Only the T allele of rs146676783 had a higher frequency in females infected with SARS-CoV-2 compared to those who were not. The carriers of the T alleles of the SNP rs146676783 had about 2.55 times the risk of being infected by SARS-CoV-2 compared to the carriers of the reference allele C and $p<0.001$.

Regarding rs146676783 genotypes, the female carriers of the CT genotype, when adjusted by age, had 2.58 times the risk of being infected by SARS-CoV-2, and the carriers of genotype TT had an odds ratio adjusted by 5.56. Inheritance model analysis showed that a dominance model transmits the T allele in females as one copy of T is enough to modify the risk. These results differ from that found in the literature, especially on the population of Asia descent, as rs146676783 or E37K is thought to reduce the binding of the S protein to the ACE2 receptor (Wang et al. 2020). We found no association between SARS-CoV-2 infection and the SNPs rs143936283 and rs4646116. However, authors have found decreased and increased SARS-Cov2 S protein binding in populations of Asian and western descent (Darbani 2020).

These differences could be due to genetic variation, as there are population-based differences between these variants (Mahmood et al. 2022; Sarangarajan et al. 2021; Srivastava et al. 2020). The haplotype analysis only yielded haplotypes among males but not in females. The latter could be due to the relatively low numbers of females after stratification, which did not allow for obtaining accuracy. It could also be due to the gender-specificity of *ACE2*. ACE2, a Renin-Angiotensin System (RAS) member, might have its gene regulated by estrogen (Wu et al. 2018). Some studies have found that ACE2 might play more prominent roles in females than males, while others found the opposite (Ahmed A. Suleiman 2021; Chen et al. 2021; Mohana et al. 2012). The location of the *ACE2* gene on the Xp22 site of chromosome X is said to have genes to prevent X chromosome inactivation and could lead to differences between genders (Berletch et al. 2011; Carrel and Willard 2005; Talebizadeh et al. 2006). The impact of the *ACE2* gene was found to be different between genders, according to several studies (Meng et al. 2015; Patel et al. 2012; Wu et al. 2018). Unfortunately, we could not gather clinical data on the COVID-19 disease and its complication related to our study subjects to further analyze their relation to *ACE2* gene SNVs studied. Additionally, a larger sample size is also needed to validate our findings.

Conclusion

This study showed that the *ACE2* gene variant rs146676783 was associated with an increased risk of being infected by SARS-CoV-2 in females in Burkina Faso. Gender-based studies are necessary to investigate the association between *ACE2* gene polymorphisms. However, polymorphisms of rs4646116 and rs143936283 showed no association with the occurrence of infection. Their expression would contribute to further understanding of why Burkina Faso and many other countries of the African continent had fewer COVID-19 cases. The proposed studies could potentially be used to develop supportive therapy for COVID-19 patients.

Abbreviations

Ab	**:**	Antibody
ACE2	**:**	angiotensin-converting enzyme receptor 2
COVID-19	**:**	Coronavirus disease 2019
ELISA	**:**	Enzyme Linked ImmunoSorbent Assay
RT-PCR	**:**	Reverse transcriptase polymerase chain reaction
SARS-CoV-2	**:**	severe acute respiratory syndrome coronavirus 2

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DECLARATIONS

CONFLICT OF INTERESTS:
The authors declare that there are no conflicts of interest**.**

ETHICS STATEMENT
The study was approved by the ethics committee for health research of Burkina Faso (CERS) (approval n° 2022-02-035). Informed Consent was obtained from the participants/parents/legal guardians in the study, for the subsequent use of the collected samples. The research has been performed in accordance with the Declaration of Helsinki. The patients' samples were handled with anonymity by using a codification system**.**

CONSENT FOR PUBLICATION
Not applicable.

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AUTHOR CONTRIBUTIONS:
TRC, IS, LT, WFD, HGO, and JS contributed to the design and implementation of the study. TRC, SZ, STS, AAZ, AKO, RK, VS, CD, ARN, OO, ZS, DK collected the data and performed laboratory testing. TRC, IS, SL, OHG, ATY, AAZ, TS performed the analysis and interpretation of data. TRC, IS, LT, and AKO drafted the manuscript. All authors commented on the manuscript. All the authors reviewed and approved the final manuscript to be published.

DATA AVAILABILITY STATEMENT:
The data sets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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