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Relationship between the Polymorphism of the *GSTP1* (rs1695) Gene and Chronic Hepatitis B Infection in Ouagadougou, Burkina Faso

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Abstract

Introduction: Genetic polymorphisms of some Glutathione S-Transferase (GST) which encode the enzyme responsible for the biotransformation of drugs and xenobiotics, have been associated with the risk of several pathologies that can progress to cancer such as Hepatitis B. This study aims to characterize the impact of the rs1695 polymorphism of *GSTP1* gene among people with chronic Hepatitis B infection in Burkina Faso. **Methods:** rs1695 polymorphisms of *GSTP1* gene genotyping was performed for 50 people infected with chronic Hepatitis B virus and 124 healthy people with the PCR-RFLP method. Conventional PCR was used for DNA amplification and Alw26I enzyme was used for enzymatic digestion. **Results:** The results show that the frequencies of AA, AG and GG genotypes are respectively 31.00%, 36.80% and 32.20% in general the study population with a mutation rate of 50.57%. However, the incidence of the AA, AG and GG genotypes are respectively 30.64%, 38.71% and 30.64% among people with chronic Hepatitis B virus infection and 32.00%, 32.00% and 36.00% among healthy people. In cases,

the frequencies of the A and G alleles are 48.00% and 52.00% respectively, and in controls 50.00% each. No statistical difference was found by comparing genotypic and allelic frequencies between cases and controls ($p > 0.05$). **Conclusion:** Our study allowed us to determine the rate of *GSTP1* rs1695 genotypes in the study population, cases and controls. From our analyses, *GSTP1* rs1695 is not associated to chronic Hepatitis B virus infection in Ouagadougou.

Keywords

Polymorphism, *GSTP1*, Chronic Hepatitis B, Healthy People, Burkina Faso

1. Introduction

Hepatitis B is a viral disease characterized by inflammation of the liver, which is potentially fatal. The Hepatitis B virus (HBV) is an enveloped DNA virus belonging to the family of *Hepadnaviridae* [1]. The virus is responsible for liver inflammation, which is usually acute or even fulminant, and could evolve either towards a cure or towards chronicity. It is a highly endemic disease, a major cause of mortality and morbidity and a major public health problem worldwide [2] [3]. According to WHO 2020, about 296 million people suffer from chronic Hepatitis B infection and around 820,000 people die each year mainly from liver cirrhosis or hepatocellular carcinoma [4].

A person is classified as a chronic case when they have had hepatitis B virus (HBsAg) antigen for more than six months [5]. And this stage of the disease affects 5% - 10% of cases in immunocompetent adults, up to 50% in the immunocompromised, and 90% in newborns infected through their mothers [5]. Persistent or chronic HBV infection is a risk factor for the development of liver cirrhosis and/or hepatocellular carcinoma (HCC) [5] [6]. According to Wagner *et al.,* 80% of hepatocellular carcinomas are caused by HBV [1]. HCC is the most common form of liver cancer worldwide and is the third leading cause of death with Hepatitis B [7]. Burkina Faso is a country with high endemicity [8] [9] with a prevalence of 9% to 14.47% in the general population [10] [11] [12] [13] and a previous study estimated the prevalence of HBV infection at 9.1% [14].

A large number of genes carrying DNA alterations have been described in the process of liver disease progression [12]. However, much work remains to be done to understand their interdependence and their predictive character in the evolution of Hepatitis. In addition, populations in sub-Saharan Africa, as elsewhere in the world, are constantly exposed to certain xenobiotic such as drugs [15], components of cigarette smoke, air pollutants, and aflatoxins [16] which increase the oxidative stress created by HBV infection. The human organism has a multi-enzyme complex capable of combating this oxidative stress and neutralising the toxic (carcinogenic) metabolites generated by xenobiotics [17]. This

mechanism is organised in three phases: 1) a first phase which includes oxidation reactions, 2) a second phase composed essentially of conjugation reactions and 3) a third phase which includes transport systems involving ABC proteins. Glutathione S-Transferase (GST, EC 2.5.1.18) is a metabolic enzyme of the multigene family of the phase II mechanism [18]. In mammals, eight classes of GSTs, namely alpha (GSTA), mu (GSTM), theta (GSTT), pi (GSTP), sigma (GSTS), kappa (GSTK), omega (GSTO) and zeta (GSTZ) have been identified on the basis of sequence homology and substrate specificity. GSTs are soluble, dimeric enzymes with a molecular weight of about 25 kDa. Each GST subunit has two binding sites: the "G" site is specific for reduced glutathione (GSH), while the "H" site is specific for the substrate itself. GSTs have well-established polymorphisms in humans. The proteins encoded by its different genes show its different capacities to metabolise carcinogens. The glutathione S transferase (GST) genes are responsible for encoding the enzymes [17] involved in the detoxification of toxic products, protecting the body against oxidative damage [19] [20]. They also play a key role in the detoxification of several endogenous and exogenous hydrophobic and electrophilic compounds [21] [22]. In recent years, the interest in studying *GSTP1* polymorphisms and the susceptibility to develop cancer becomes inevitable. Given the wide variation in *GSTP1* allele frequencies in different ethnic populations, several studies have been carried out to determine *GSTP1* polymorphisms and the risk of different cancers [23] [24] [25] [26] [27].

In Burkina Faso, to our knowledge, no study has yet been done on *GSTP1* gene polymorphisms in chronically infected Hepatitis B seropositive patients. The main objective of this study was to investigate the association of genetic polymorphisms of the Glutathione S-Transferase P1 rs1695 with chronic Hepatitis B infection in Ouagadougou, Burkina Faso.

2. Methods

2.1. Study Design and Sampling

This is an analytical case-control study including 50 seropositive persons for chronic Hepatitis B infection considered as cases and 124 seronegative persons for viral Hepatitis B, viral Hepatitis C, HIV/AIDS and Syphilis as controls. No age, gender or socio-demographic criteria were imposed. The study took place in Ouagadougou, the capital of Burkina Faso and was conducted over a period of sixteen (16) months from March 2021 to June 2022. The collection of control samples was done at the National Blood Transfusion Centre (CNTS) and the collection of case samples was done at the Biomolecular Research Centre Pietro Annigoni (CERBA). All the molecular biology analyses were carried out in the Laboratory of Molecular Biology and Genetics (LABIOGENE) of the Joseph KI-ZERBO University. The Institute of Research in Health Sciences (IRSS/CNRST) provided support in terms of equipment for the various manipulations.

Chronic Hepatitis B was defined when the person has been a carrier of Hepatitis B virus antigen (HBsAg) for more than six months. Blood samples were taken in EDTA tubes and then centrifuged. The supernatant was separated from the

pellet for viral load testing and the pellet was used for genomic DNA extractions.

To ensure that we had samples chronically infected with hepatitis B, some doubtful patients were discarded. All the chronic HBV samples which have no amplification of the Human Growth Factor control during PCR were discarded.

2.2. DNA Extraction

DNA extraction was performed at LABIOGENE using the Rapid Salting-Out technique [28]. The principle is based on cell lysis, digestion and precipitation of proteins, washing of impurities and elution of DNA.

2.3. Characterisation of the *GSTP1* rs1695 Gene Polymorphisms by RFLP PCR

Genotyping of the *GSTP1* polymorphism was performed using the PCR-RFLP method as described by Abbas *et al.* [29]. The PCR-RFLP (polymerase chain reaction restriction fragment length polymorphism) approach is based on the comparison of restriction enzyme cleavage profiles following the existence of a polymorphism in the sequence of a DNA molecule already amplified by PCR. Mutations in a DNA sequence recognized by a restriction enzyme will result in different restriction fragment lengths. The PCR product is then digested by one or more restriction enzymes. The restriction fragments are then separated on an agarose gel for genotyping. Restriction enzymes are endonucleases that specifically recognize a short sequence of 4 or 8 bases and cut the DNA chain each time they recognize this elementary sequence. The DNA is thus fragmented into pieces of different lengths, separated according to their size by electrophoresis.

Briefly, we used the 9700 system to perform a PCR with a 25 µL reaction mixture containing for each sample 5 µL of DNA; 5 µL of 5x FIREPol "Master Mix Ready to Load"; 0.5 µL of each of the 1/2 strength primers (Table 1) and 14 µL of H_2O.

GSTP1 Initial denaturation was performed at 95˚C for 5 min, followed by 50 cycles at 94˚C for 30 s (second denaturation), 63˚C for 30 s (hybridization), 72˚C for 40 s (elongation), a final step of 72˚C for 7 min was performed for a final extension.

Two grams of agarose powder were suspended in 100 mL of 1X Tris Acetate EDTA buffer (1X TAE). The resulting solution was then boiled by heating in the microwave for five minutes with careful stirring at half-time. The heated suspension was cooled to room temperature, 18 µL of Ethidium Bromide (BET) (10 mg/mL) was added and homogenised. The resulting mixture was poured into an electrophoresis tray on which combs were placed to obtain wells after solidification of the gel (2%) at room temperature.

Table 1. Sequences of primers specific to the amplification of the *GSTP1* gene.

Gene	Primer	Enzyme	Size of the fragments
GSTP1 **Rs1695**	5'-ACCCCAGGGCTCTATGGGAA-3' 5'-TGAGGGCACAAGAAGCCCCT-3'	Alw26 I	176 base pairs

The gel was placed in the electrophoresis tank containing migration buffer. The PCR product from each sample of 5 µL volume was deposited into the gel wells ensuring that the gel was immersed in the migration buffer (TAE 1X). In one of the wells, 5 µL of 100 bp Ladder molecular weight marker was deposited. The electrophoresis tank was placed under a voltage of 100 Volt (V) at 50 milliamperes (mA) for 15 minutes thanks to a voltage generator allowing the separation of the DNA fragments according to their molecular weight. Development was carried out under UV light using a Gene flash device (the trans-illuminator), the images of which were recorded.

Unlike the preparation of the 2% agarose gel, we dissolved three (03) grams of agarose in 100 ml of 1X TAE.

The restriction enzyme Alw26I is naturally derived from the *Acinetobacter lwoffii* strain RFL26. It recognises the 5'GTCTC3' and 3'CAGAG5' sites and cuts at the first and fifth nucleotide after the recognition sequence. In our study, the restriction enzyme Fastdigest Alw26I (Ils class) Thermo Scientific FD0034 was used for digestion according to the reaction mixture of a total volume of 30 µL per sample containing: H_2O without nuclease: 17 µL; 10X fastdigest buffer: 2 µL; PCR product: 10 µL; fastdigest enzyme: 1 µL. The reaction volume was thoroughly mixed and then incubated at 37˚C for 4 hours and at 65˚C for 20 minutes to inhibit enzyme activity.

In contrast to the electrophoresis and UV revelation of the PCR products, for the digestion products we used a 3% agarose gel.

The PCR amplification is considered valid if the sample shows a band corresponding to 176 bp. It is invalid in the absence of this band. The digestion is valid if the sample has either one band of 176 bp, two bands of 91 bp and 85 bp or three bands of 176 bp, 91 bp and 85 bp.

During our manipulations, we used Human Growth Factor (HGF) for quality control of our PCR.

2.4. Data Analysis

Data were entered into Excel 2016 and analysed using Statistical Package for Social Sciences (SPSS) version 21.0. Chi-square test and odds ratio (OR) were used for comparisons with 95% confidence interval. The difference was statistically significant for $p < 0.05$.

2.5. Ethical Considerations

The protocol obtained the approval of the Health Research Ethics Committee (CERS) by deliberation number 2019-5-067 of 15 May 2019. Confidentiality and anonymity with regard to the information obtained in the various patient registers were respected.

3. Results

This study included 174 samples of which 71.30% were seronegative for Hepati-

tis B infection and 28.70% were seropositive for chronic Hepatitis B infection. Sixty-four point four percent (64.40%) of our population was male and 35.60% was female. Approximately 48.00% of the chronic Hepatitis B seropositive patients did not specify a treatment regimen and 24.00% were on tenofovir therapy monitored by a physician. Very few patients (6.00%) were on conventional treatment (Table 2).

The age of the population varied from 4 to 55 years with an average of 31.44 ± 9.61 years. The age group 20 to 29 years is the most represented in our study population at 47.10% (Table 3).

Figure 1 shows the results found after UV revelation of the PCR and digestion products. The PCR products were 176 bp (Figure 1(a)). Figure 1(b) shows the different genotypes found. Wells 1, 4 and 12 show a single band of 176 bp for the AA genotype. Wells 3, 5 and 9 show two bands of 85 bp and 91 bp for the GG genotype and wells 6, 7 and 11 show three bands of 176 bp, 91 bp and 85 bp for the AG genotype (Figure 1(b)).

The frequency of AA, AG and GG genotypes were 31.00% (54/174), 36.80% (64/174) and 32.20% (56/174) respectively in the study population. The frequency of A and G alleles were 49.43% and 50.57% respectively (Figure 2).

Table 2. Demographic distribution by gender and treatment.

	Workforce	Rates (%)	p-value
SEX			
Female	62	35.6	**<0.001**
Male	112	64.4	
TREATMENT			
Tenofovir	12	24.0	**0.003**
Traditional	3	6.0	
No treatment	11	22.0	
Not specified	24	48.0	
Holy subjects (Witnesses)	124	71.26	

Table 3. Demographic distribution by age group.

Age	Case n (%)	Control n (%)	Total n (%)	p-value
<20	4 (8.0)	4 (3.22)	8 (4.6)	<0.001
20 à 29	11 (22.0)	71 (57.26)	82 (47.1)	
30 à 39	11 (22.0)	28 (22.58)	39 (22.4)	
40 à 49	22 (44.0)	18 (14.51)	40 (23.0)	
50 and over	2 (4.0)	3 (2.42)	5 (2.9)	
Total	50 (100.0)	124 (100.0)	174 (100.0)	

n = workforce; % = Frequencies.

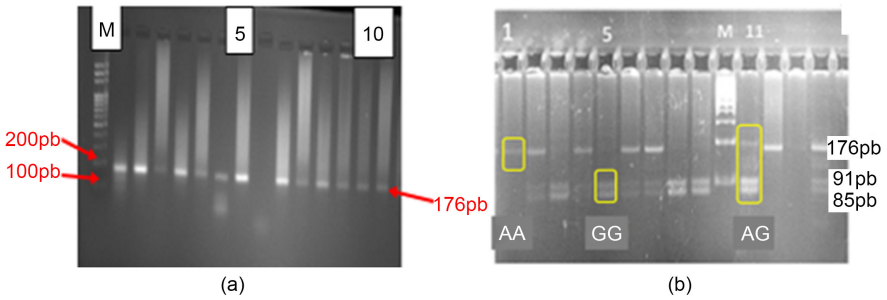

Figure 1. Electrophoresis gel products. Legend: (a) Electrophoresis gel of PCR products. (b) Electrophoresis gel of digestion products. M: Molecular weight marker; bp: base pair.

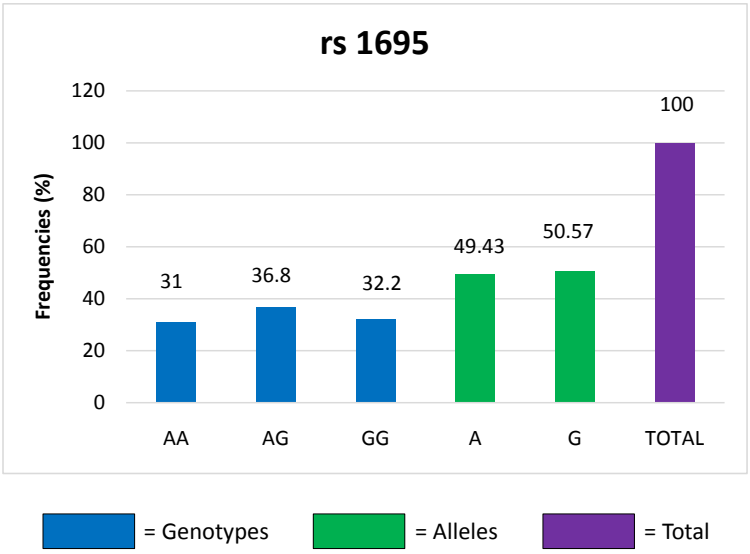

Figure 2. Genotypic and allelic frequency (*GSPT1* rs1695) in our study.

We did not observe any association (p = 0.475) between *GSTP1* genotypes (rs1695) and the demographic trait "age" but an association between *GSTP1* genotypes and treatment (Table 4).

Table 5 shows the distribution of the different genotypes in cases and controls. There is no association between *GSTP1* genotypes and chronic Hepatitis B infection. None of the *GSTP1* genotypes appears to be a risk or protective factor for chronic Hepatitis B infection.

4. Discussion

Our study consisted in characterising for the first time in a population of the Burkinabe capital, the genotypes of the *GSTP1* rs1695 gene.

The 20 - 29 age group, representing about 47.10% of our study population, is more represented. The average age was 31.44 ± 9.61 years. Our results were close to those found by Sombié *et al.* in their study on chronic Hepatitis B treatment at the Yalgado-Ouédraogo University Hospital, Ouagadougou, Burkina Faso in 2015 who found an average age of 40 years [30]. Sawadogo *et al.* in their study on HBV carriage at the Sanou Sourou University Hospital in Bobo-Dioulasso

Table 4. Genotype frequencies of *GSTP1* by demographic traits.

	Genotypes			p-value
	AA n (%)	**GA n (%)**	**GG n (%)**	
Age category				
<20	4 (7.40)	4 (6.25)	0 (0.00)	
20 à 29	27 (50.00)	31 (48.44)	24 (42.86)	
30 à 39	12 (22.22)	15 (23.44)	12 (21.42)	0.47
40 à 49	10 (18.52)	12 (18.75)	18 (32.14)	
50 and over	1 (1.85)	2 (3.12)	2 (3.57)	
Treatment				
Not specified	9 (56.25)	5 (31.25)	10 (55.55)	
No treatment	3 (18.75)	3 (18.75)	5 (27.77)	<0.001
Tenofovir	3 (18.75)	6 (37.50)	3 (16.67)	
Traditional	1 (6.25)	2 (12.50)	0 (0.00)	

n = Staff; % = Frequencies.

Table 5. Genotypic and allelic frequency of *GSTP1* in cases and controls.

Genotypes n (%)	**Controls n (%) n = 124**	**Cases n (%) n = 50**	**OR (95% CI)**	**p-value**
AA 54 (100)	38 (30.64)	16 (32.0)	Ref	Ref
AG 64 (100)	48 (38.71)	16 (32.0)	0.745 (0.372 - 1.494)	0.406
GG 56 (100)	38 (30.64)	18 (36.0)	1.276 (0.637 - 2.544)	0.494
AG/GG 51 (100)	86 (37.25)	34 (62.64)	0.970 (0.595 - 1.583)	0.904
Allèles				
A	124 (50.0)	48 (48.0)	1.061 (0.712 - 1.582)	0.771
G	124 (50.0)	52 (52.0)		

OR: Odd Ratio; 95% CI: 95% confidence interval.

found a mean age of 43.60 ± 8.20 years showing a non-significant variation in mean age across localities [31]. The prevalence of HBV in males (12.06%) was lower than those in females (16.60%) and the difference was statistically significant ($p < 0.001$). This does not corroborate with the studies conducted by Tao *et al.* in 2014 in Ouagadougou who found that the prevalence of HBV in men (18.58%) was higher than those in women (11.60%) with a p-value = 0.002 [10]. This difference can be explained by the different sample sizes of the two studies.

Although most of our patients did not specify their treatment or did not even have a current treatment, we observed that only treatment with tenofovir was recommended (24.00% with a $p \leq 0.003$) by physicians to the detriment of other molecules such as nucleoside or nucleotide analogues (Lamivudine, Adefovir…),

Interferon (α2a and 2b), Pegylated interferon (IFN PEG α2a) available on the market. This can be explained by the resistance profile of tenofovir, its antiviral efficacy and its availability on the market, which is clearly superior to other molecules [32]. Sombié *et al.,* in their comparative study between the different treatments for chronic Hepatitis B, in particular between tenofovir and lamivudine at the Yalgado-Ouédraogo teaching Hospital, Ouagadougou, Burkina Faso in 2015, confirmed the efficacy of tenofovir: undetectable viral load at 89.6% in the tenofovir group and 75% in lamivudine patients; no resistance was observed with tenofovir but with lamivudine, the resistance rate was at 1 year 13%, 2 years 24%, 3 years 34.80%, 4 years 46.30% and 5 years 59.80% [30]. In the present study, the genotypic frequencies of GSTP1 rs1695: AA, AG and GG were 31.00%; 36.80% and 32.20% respectively. The frequency of the heterozygous AG genotype, at 36.80%, was higher than that of the other genotypes (including GG greater than AA). Our results corroborate to those observed in Mali by Kassongue *et al.* who had worked on the genetic polymorphisms of GST in the general population of Mali, where the prevalence of the AA, AG, GG genotypes was respectively 27.73%; 49.03%; 25.24% with a higher frequency of AG followed by GG then AA [33]. These two studies show a high frequency of the AG genotype. This could be explained by the different common exposures especially climatic in these two regions.

However, we noted that the frequency of the double mutation is 3 to 6 times higher than that observed by Valeeva *et al* in Russia in their study on GST polymorphisms and the risk of liver damage in 2019 [34]. The same observation is noted with Barros *et al.* in Brazil on lateral sclerosis where they found 5.90% GG in cases and 12% GG in controls [35]. These studies showed a low rate of the *GSTP1* rs1695 gene double mutation in the study populations in contrast to our results. This difference in the frequency of the double mutation could be explained by the effects of different climate exposures, lifestyle for adaptation of the human species depending on the regions, race (white population and black population) and socio-cultural traditions of each people [36].

GSTP1 plays a central role in the inactivation of toxic and carcinogenic electrophiles [36]. GSTP1 enzymatic activity is significantly lower in individuals with the 105Val allele due to the nucleotide 313 polymorphism in the *GSTP1* gene causing a decrease in enzymatic activity and reducing the ability to metabolise certain xenobiotics and carcinogens [27]. Biochemical studies have indicated that the GG genotype of GSTP1 is 2 - 3 times less stable [37] and may be associated with cancer risk [38]. Palma *et al.* in 2010 suggested that the homozygous *GSTP1* genotype, independent of smoking, appears to be associated with a 5.7-fold increased risk of developing cancerous lesions [39].

In our present study, the frequencies of the AA, AG and GG genotypes are 30.64%, 38.71%, 30.64% in controls and 32.00%, 32.00% and 36.00% in cases respectively. The frequencies of the A and G alleles were 48.0% and 52.00% respectively in the cases and 50.00% each in the controls. GSTP1 IIe/val (A/G) and val/val (GG) genotypes, carrying a mutant allele, were more frequent in patients

with chronic Hepatitis B infection than in healthy controls respectively (OR: 0.745, 95% CI (0.372 - 1.494); p = 0.406); (OR = 1.276, 95% CI (0.637 - 2.544); p = 0.494).

Our results do not corroborate those of Kandemir *et al.* in Turkey who found that *GSTP1* IIe/val (A/G) and val/val (GG) genotypes were significantly more frequent in patients with chronic Hepatitis B infection (OR: 1.909, 95% CI 0.993 - 3.668; p = 0.049) (OR = 6.799, 95% CI 1.712 - 26.99; p = 0.006) than in healthy controls [40]. The differences between our results and this study can be justified by the difference in sample sizes on the one hand, and by the ethno-geographical differences of the study populations on the other.

Our results show that *GSTP1* rs1695 polymorphisms and the A and G alleles are not associated with chronic Hepatitis B infection in our study population (OR = 1.061, 95% CI (0.712 - 1.582); p = 0.771).

5. Conclusion

This study allowed us to characterise the rs1695 polymorphisms of the *GSTP1* gene in individuals seropositive for chronic Hepatitis B infection in Ouagadougou. From a genetic point of view, the [G] allele resulting from the mutation (AG and GG) of *GSTP1* was the most frequent but is not associated with chronic Hepatitis B infection. This study providing information on the *GSTP1* rs1695 genotype in a population sample from Ouagadougou shows that *GSTP1* rs1695 polymorphisms do not appear to be involved in chronic Hepatitis B infection. Although this study is relevant because of the consequences of chronic Hepatitis B infection worldwide, the sample size does not allow conclusions to be generalised to the entire Burkinabe population. A large study is needed to confirm our results.

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Data Availability Statement

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

Ethical Statement

Our study obtained the approval of the Ethics Committee for Health Research (CERS) of Burkina Faso (Deliberation n˚ 2019-5-067 of 15 May 2019).

Information on Consent

The participants gave their free and informed consent. Every effort was made to

preserve not only the privacy but also the confidentiality, dignity and honour of the patients.

Conflicts of Interest

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

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