RESEARCH ARTICLE

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Genotype and Association of *XRCC1* Gene With Liver Disease in Chronic Hcv Patients

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Abstract

Chronic infections with hepatitis B virus (HBV) and hepatitis C virus (HCV) are well-established major risk factors for hepatocellular carcinoma (HCC). Nevertheless, only a minority of infected individuals progress to HCC in their lifetime, highlighting the potential influence of genetic factors in modulating susceptibility to this malignancy. The X-ray repair cross-complementing group (*XRCC1*) is involved in DNA repair pathways. **Aim:** investigate the association between the c.24589 G>A single nucleotide polymorphism (SNP) of the *XRCC1* gene and the risk of developing hepatocellular carcinoma (HCC) in patients with chronic hepatitis C virus (HCV) infection. **Methods:** A case-control study was conducted in the oncology departments of Peshawar, Pakistan, involving 30 HCC patients and 30 cirrhotic HCV patients without HCC. After collecting relevant clinical data and basic laboratory tests,c.24589 G>A SNP of the *XRCC1* gene was analyzed using the ARMS-PCR technique. **Results:** A statistically significant higher frequency of *XRCC1* (AA and GA) genotypes was observed in patients with hepatocellular carcinoma (HCC) compared to those with cirrhotic hepatitis C virus (HCV) ($p = 0.0425$). In addition, the A allele frequency was notably higher in the HCC group (54% compared to 23%, $p = 0.0178$). Moreover, multivariate analysis indicated that the c.24589 G>A SNP independently increased the risk of developing HCC by 4.58 times (95% CI: 1.7–11.88, $p = 0.017$). Furthermore, patients with the AA and GA genotypes displayed larger tumor sizes ($p = 0.008$), a greater number of tumor foci ($p = 0.006$), and higher Child-Pugh grades ($p = 0.044$). **Conclusion:** *XRCC1* gene polymorphism could be associated with increased risk of HCC development in chronic HCV patients.

Keywords: *XRCC1*- SNP- c.24589 G>A- Hepatocellular carcinoma- HCV- ARMS - DNA repair

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Introduction

Chronic HCV infection is a significant public health concern, particularly in Pakistan, where it is a leading cause of chronic liver disease and hepatocellular carcinoma (HCC) [1]. Notably, HCC , as well as in many other regions [2]. Its development is influenced by a complex interplay of genetic and environmental factors, including viral infections and toxin exposure. Among these, genetic factors such as *XRCC1* gene polymorphisms play a critical role in DNA repair. Alterations in this gene can significantly increase the risk of HCC, and the higher prevalence of *XRCC1* polymorphisms in advanced stages of HCC further suggests their involvement in disease progression. This association is likely due to impaired DNA repair mechanisms that permit the accumulation of mutations [3].

HCC is the most prevalent type of liver cancer, accounting for nearly 90% of liver cancer cases globally [4]. The primary contributors to HCC include chronic hepatitis B or C infections, excessive alcohol consumption, and exposure to toxins, all of which exacerbate liver damage [5]. Consequently, understanding these factors is essential for developing better screening and prevention strategies for at-risk populations. Moreover, the *XRCC1* gene, which plays a pivotal role in the base excision repair (BER) pathway, is often implicated in cancer risk. Genetic mutations in *XRCC1* can disrupt DNA repair processes, further increasing the likelihood of cancer development [6]. Recent studies have highlighted the role of genetic factors, including *XRCC1* polymorphisms, in HCC progression. These polymorphisms not only contribute to cancer risk but also influence treatment outcomes and survival rates in HCC patients [7].

Specifically, the *XRCC1* Arg280His variant has been associated with an elevated risk of HCC across different

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populations, emphasizing the importance of preventive measures, particularly in Pakistan. Individuals carrying the Arg/His genotype of *XRCC1* Arg280His are at a greater risk of developing HCC than those with the Arg/Arg genotype [8]. Furthermore, previous research has identified a significant correlation between HCC and specific single nucleotide polymorphisms (SNPs) in the *XRCC1* gene, such as Arg194Trp and Arg280His. The combination of these SNPs has been shown to amplify the risk of HCC further [9]. In this context, the present study aims to investigate common *XRCC1* genotypes and their association with the heightened risk of HCC among patients with chronic HCV infection in Peshawar, Pakistan. Particular attention will be given to the Arg280His mutation located in exon 9 of the *XRCC1* gene, which spans 33 kb, consists of 17 exons, and encodes a 70 kDa protein located on chromosome 19q13.2-13.3 [10].

Materials and Methods

This case-control study was conducted at the oncology departments of Kuwait Teaching Hospital (KAUH), Khyber Teaching Hospital, and Hayatabad Medical Complex in Peshawar, Khyber Pakhtunkhwa, between February 2024 and June 2024. The study received approval from the Institutional Review Board (IRB) Committee of the Hayatabad Medical Complex on February 2, 2024. Specifically, a total of 30 patients with hepatocellular carcinoma (HCC) secondary to chronic HCV infection and 30 post-hepatitis C cirrhotic patients were enrolled.

The diagnosis of HCC was established based on several factors, including medical history, clinical examination, and radiological investigations, which involved abdominal ultrasound and triphasic computed tomography (CT) of the abdomen. Additionally, laboratory investigations were performed, including tests for hepatitis B and C markers, as well as alpha-fetoprotein (AFP) levels. Patients with other causes of liver cirrhosis and HCC, such as chronic HBV infection, metabolic liver diseases, autoimmune liver diseases, fatty liver disease, and alcoholic liver diseases, were excluded from the study.

Moreover, the study protocol was approved by the local ethics committee of Peshawar University, and informed consent was obtained from all patients and control subjects before the commencement of the study.

Routine Laboratory Investigations

After collecting clinical data, laboratory tests were performed. These included:

• Complete blood counts (CBC): Analyzed using the Sysmex XT-1800i Automated Hematology Analyzer (Sysmex Corporation, Kobe, Japan).

• Liver function tests (LFTs): Conducted using the Cobas 6000 autoanalyzer (Roche Diagnostics, GmbH, Mannheim, Germany).

• Prothrombin concentration and INR: Measured with the BFT II Analyzer (Dade Behring, Marburg, Germany).

• Hepatitis serology: Including HBsAg and HCV Ab testing.

• Serum alpha-fetoprotein levels: Determined using the Cobas e411 immunoassay analyzer (Roche Diagnostics, GmbH, Mannheim, Germany).

DNA Extraction and Genotyping

Venous blood samples were collected from all participants, and genomic DNA was subsequently extracted using the Transgenic DNA Kit. In order to identify *XRCC1* c.24589 polymorphisms, the polymerase chain reaction-restriction fragment length polymorphism (PCR-ARMS) method was utilized, as described by Bi et al. (2013). This method was chosen due to its reliability and efficiency in detecting single nucleotide polymorphisms.

For the amplification process, a 227-base-pair (bp) fragment was generated in a reaction volume of 25 µL. Specifically, this mixture included 1 µL of each primer—wild reverse (5'-CCAGTGCCAGCTCCAACTAG-3'), mutant reverse (5'-CCAGTGCCAGCTCCAACTAA-3'), and common reverse (5'-TACTTGGCCCCAAGCTCTAG-3')—in addition to 12.5 µL of Blue Mix Master Mix (2X; Bioline, MA, USA), 5.5 µL of nuclease-free water, and 2.5 µL of extracted genomic DNA.

Furthermore, the PCR amplification was performed using a pre-programmed thermal cycler (Perkin Elmer GeneAmp PCR System 2400 Thermal Cycler, version 2.11, USA). The protocol consisted of an initial denaturation step at 94°C for 5 minutes, followed by 35 cycles of denaturation at 95°C for 35 seconds, annealing at 58°C for 35 seconds, and extension at 72°C for 35 seconds. Lastly, a final extension step at 72°C for 5 minutes was carried out to ensure the complete amplification of the target fragment.

Statistical Analysis

All statistical analyses were conducted using the Statistical Package for Social Studies (SPSS) software (version 25, Chicago, IL, USA). To compare differences in *XRCC1* Arg280His between the cirrhosis and HCC groups, a Student's unpaired t-test was utilized, with a p-value of less than 0.05 considered statistically significant. Furthermore, the correlation between the SNP and HCC risk was evaluated using the Chi-square test, ensuring robust statistical validation. In addition, multivariate binary logistic regression analysis was applied to investigate the effect of various independent variables, including age, gender, AFP, LFTs, allele mutation, normal mutation, *XRCC1* genotypes (GA+AA), tumor size, and Child-Pugh classification, on HCC risk. This comprehensive approach allowed for the identification of significant predictors and their contributions to the overall risk assessment.

Results

Demographic and laboratory data of the studied groups

Demographic and laboratory data of the studied groups Neither age nor gender distribution were different between the two study groups (Table 1). Looking closer at the blood test results (Table 2), there were clear differences between the HCV and HCC groups. The HCC group had abnormal results in several parameter, including lower

Table 1. Demographic and Laboratory Data of the Studied Groups

Characteristic	Group I (Cirrhosis) (n = 30)	Group II (HCC) (n = 30)	Test of Significance (P-value)
Gender			0.3922
Male	20 (67%)	13 (43%)	
Female	10 (33%)	17 (57%)	
Age			
Mean ± SD	57.0 ± 18.0	60.0 ± 11.0	

χ^2 ; p, χ^2, and p values for Chi-square test for comparing between the two studied groups.

platelet counts, signs of liver damage in their liver tests, and elevated levels of AFP, a tumor marker. Interestingly, the liver cancer (HCC) group had even higher levels of AST, an enzyme linked to liver cell damage, and AFP, a tumor marker, compared to the cirrhosis group. On the other hand, their albumin levels, a protein important for maintaining fluid balance, were significantly lower. This suggests that while both groups have liver damage, the damage in the HCC group might be more severe. Interestingly, some tests like platelet count, blood clotting ability (INR), another liver enzyme (ALT), bilirubin levels (waste products from red blood cells), and another enzyme (ALP) didn't show any significant difference between the HCC and cirrhosis groups.

XRCC1 genotype distribution and allele frequency among studied groups

The genotype distribution indicates significant differences between the cirrhosis and HCC groups, with a significant p-value of 0.0425 for the AA genotype. There are 24% of individuals with cirrhosis with the AA genotype (two A alleles), whereas only 60% of people with HCC carry the AA genotype. In contrast, GG genotypes (no A alleles) are found in 20% of cirrhosis patients, and 30% of HCC patients. Additionally, the A allele frequency is significantly higher in the HCC group (54% compared to

Table 2. Analysis of Different Parameters of Cirrhosis and HCC Patients

Variable parameter	Group I (cirrhosis) (n=30)	Group II (HCC) (n=30)	Significant P (=0.05)
Platelets ($\times 10^3/\mu l$):			
Range	411	392 .0	
Median	212	235	0.059
INR			
Range	1.12 – 2.54	1.07 – 4.50	0.297
Median	1.55	1.58	
AST (IU/L)			
Range	52	643	0.074
Median	379	61	
ALT (IU/L)			
Range	199	35	
Median	41	77	0.296
ALP (IU/L)			
Range	442	54. 0	
Median	229	384	0.17
Albumin (g/dl)			
Range	2.94	5.9	0.177
Median	3.78	3.5	
Total bilirubin (mg/dl)			
Range	4.28	16.88	0.045
Median	1.97	1.84	
Direct bilirubin (mg/dl)			
Range	2.98	1.75	0.193
Median	0.5	0.5001	
AFP (ng/mL)			
Range	0	13218	0.03
Median	1	300	

INR, (International Normalized Ratio); AST, (Aspartate aminotransferase); ALT, (Alanine aminotransferase); ALP, (Alkaline phosphatase); AFP, (alpha-fetoprotein) were evaluated; and their respective p-values were obtained using t-tests.

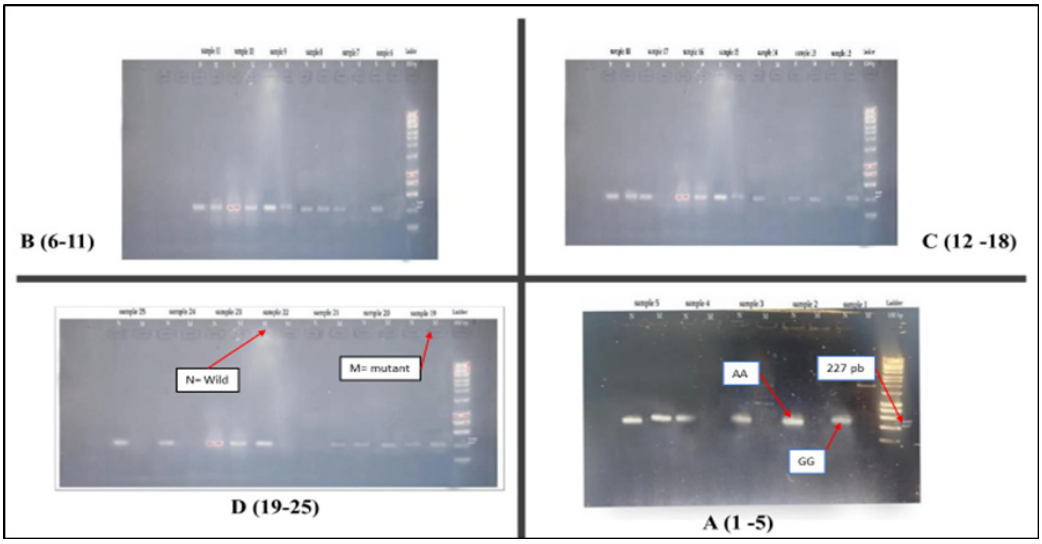

Figure 1. Agarose Gel Electrophoresis Images of Extracted Samples for HCC FROM (1-25)

Table 3. Distribution of *XRCC1* (rs.24589G>A) Genotype and Allele Frequencies among the Studied Groups

	Group I (cirrhosis) (n = 30)		Group II (HCC) (n = 30)		$\chi 2$	Test of significance P-value
	No.	%	No.	%		
Genotypes						
GG	10	-20%	14	-30%	20.74	0.1999
GA	8	-38%	13	-28%		0.1999
AA	12	-24%	3	-60%		0.0325
GA+AA	20	-40%	16	-34%	0.82	0.177
Alleles						
G	17	-46%	27	-63%		
A	20	-54%	16	-37%	0.0156	

The χ^2 and p-values were calculated for the Chi-square test to compare between the two groups. Significance among the groups was assessed using Fisher's Exact test. An asterisk (*) denotes statistical significance at $p \leq 0.05$. Additionally, p1 represents the p-value for comparing groups I and II.

23% in cirrhosis), with a p-value of 0.0178. This suggests an association between the A allele and an increased risk of developing HCC. The results of the PCR-ARMS analysis for the XRCC1 (rs.24589G>A) polymorphism were visualized using agarose gel electrophoresis, as shown in Figure 1 for HCC patient samples (1-25) and Figure 2

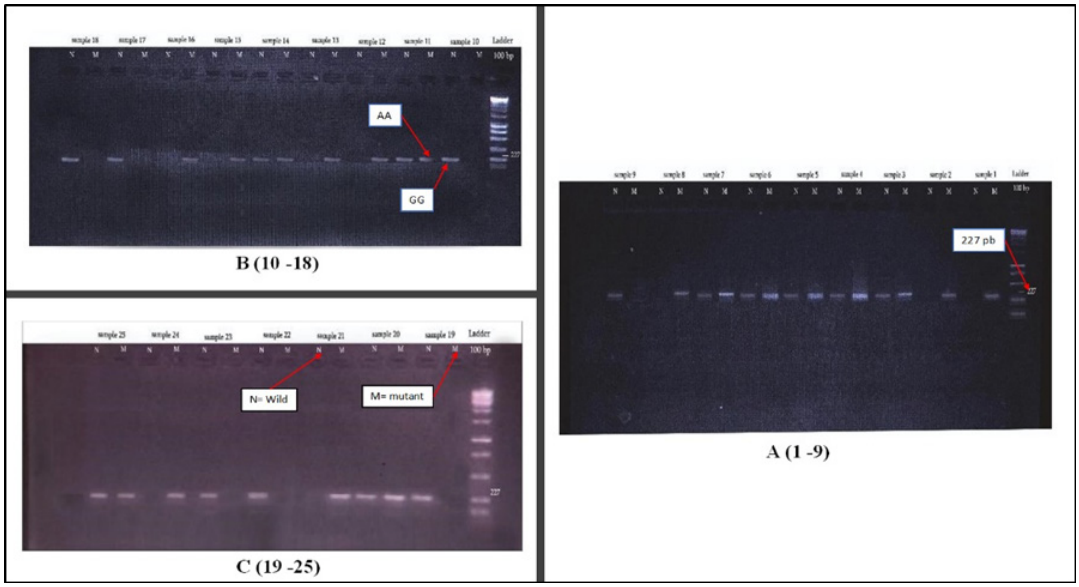

Figure 2. Agarose Gel Electrophoresis Images of Extracted Samples for HCV and Analyzed by ARMS – PCR FROM (1-25).

Table 4. Univariate and Multivariate Logistic Regression Analysis for HCC Cases

	Univariate Analysis			
	P value	OR	95% CI	
			Lower	Upper
Age (years)	0.464	2.88	0.97	1.23
Gender	0.39	1.9	0.18	1.9
Viral load	1.09	2	1	1
XRCC1 genotypes (GA+AA)	0.18	3.74*	0.2	1.55
Child-Pugh Classification (B +C)	0. 94	3.09	0.86	10.79
	Multivariate Analysis			
	P value	Adjusted OR	95% CI	
			Lower	Upper
Viral load	0.04	1.73	1.7	1
XRCC1 genotypes (GA+AA)	0.017	4.58*	0.2	1.87
Child-Pugh Classification (B +C)	0. 44	4.07	0.86	11.88

CI, Confidence interval; OR, Odds, (*) Odd Ratio considering GG as reference.

Table 5. Comparison of *XRCC1* Genotypes Regarding HCC Characteristic

Genotype GG N = (14)			Genotype GA+AA N = (16)			
	No.	%	No.	%		Test of significans P – value
N.foci Single	5	19	10	19	$\chi 2$ =9.75	P=0.006
Multiple Size (cm)	8	31	17	40		
Max. – Min	1.54 – 5.60		2.0 – 11.0	U=27.50		P=0.008
SD ± Mean	2.72 ±1.17		5.17 ± 2.39			
Median	2.3		4			
Child-Pugh classification						Test of significans P –value
	No.	%	No.	%		
A	1	8.2	4	12.1	χ^2 =4.00	P = 0.044
B	1	42.9	4	12.1		
C	3	18.6	25	75.8		

χ^2, p: Chi-square test values and corresponding p-values; FEp: p-value for Fisher's Exact test in the context of Chi-square tests; U, p: Mann-Whitney test values and associated p-values; *: Statistically significant at $p \leq 0.05$.

for HCV patient samples (1-25), illustrating the genotype distributions in both groups.

XRCC1 gene polymorphism and the risk of hepatocellular carcinoma

Univariate analysis indicated that the AA and GA genotypes were linked to a 3.74-fold higher risk of developing hepatocellular carcinoma (HCC) compared to the GG genotype. Multivariate analysis further revealed that the *XRCC1* (rs2458 G>A) polymorphism independently increases the risk of HCC in chronic hepatitis C virus (HCV) patients by 4.96 times (Table 4). Additionally, patients with AA and GC genotypes exhibited a significantly higher number of tumor foci (p=0.006), larger tumor sizes (p=0.008), and more advanced Child-Pugh grades (p=0.044) (Table 5). To investigate whether the AA homozygous genotype independently influences focal lesions in HCC patients, we compared the characteristics of focal lesions between those with the rs.2589G>A AA genotype and those with GA and GG genotypes. The results showed no significant differences between the two groups regarding the number of foci or focal lesion size (p=1.000 and p=0.805, respectively). Additionally, no significant difference was found in ChildPugh classification (p=0.497).

Discussion

The development of HCC can be influenced by factors related to population or individual susceptibility, including variations in tumor-related genes such as those involved in DNA repair and metabolic processes [11]. SNPs in these genes can lead to varying levels of susceptibility to carcinogens [12]. Polymorphisms in DNA repair genes that impair or reduce DNA repair capacity can elevate the risk of mutations and cancer development [8]. Studies have shown that individuals with Arg/His genotype of *XRCC1* Arg280His have a higher risk of developing HCC than individuals with the more common Arg/Arg genotype [13]. Previous studies have suggested that there is a significant association between hepatocellular carcinoma (HCC) and various single nucleotide polymorphisms in the *XRCC1* gene. This study found an association between

certain *XRCC1* genotypes and increased risk of hepatitis virus associated hepatocellular carcinoma (HCC) in Indians [14]. Specifically, Arg194Trp and Arg280His genotypes were found to increase the risk of HCC by 2.27- and 4.95-fold, respectively [15]. Therefore, when the Arg280XHis genotype is found together with his Arg194Trp and Arg399Gln, the risk of hepatocellular carcinoma increases further, with a 5.28-fold increased risk [15]. Another ponder found that Arg194Trp and Arg280His genotypes were related with expanded hazard of hepatocellular carcinoma. This chance was advance expanded when the The Arg280His genotype has been associated with the Arg194Trp and Arg399Gln genotypes [16]. Our study aimed to investigate the relationship between the *XRCC1* (rs.24589 G>A) polymorphism and the risk of HCC in Pakistani patients with chronic HCV infection. This hereditary variation speaks to a non-synonymous to C transformation in exon 14 of the *XRCC1* This genetic variation results in the replacement of arginine (Arg) with histidine (His) at position 280.We observed a significantly higher frequency of *XRCC1* (AA, GA) genotypes in patients with cirrhotic HCV (40%) compared to those with HCC (34%), with the G allele being more prevalent in the cirrhotic HCV group (72%). Multivariate analysis indicated that the *XRCC1* (rs24589 G>A) polymorphism is an independent risk factor for the development of HCC in chronic HCV patients, increasing the risk by 4.58 times. Additionally, patients with AA and GA genotypes exhibited a greater number and larger size of tumor foci, as well as more advanced Child-Pugh 30 grades. This finding is consistent with the study by Khaled et al. (2012), which investigated the c.24589G>A and c.1254C>T polymorphisms in the *XRCC1* gene among the Chinese Han population with HCC. They reported a significant association between the *XRCC1* (AA, GA) genotypes and HCC risk, with AA, GA, and GG genotypes representing 0.1%, 31.0%, and 31.0% of the HCC group, respectively. The AA/GA genotypes were associated with an increased risk of HCC (OR 0.0991, $p < 0.05$).

However, they did not find a significant difference in the number of tumor foci, tumor size, or Child-Pugh classification between HCC patients with the AA homozygous genotype and those with GA or GG genotypes. In conclusion, the *XRCC1* (c.24589)AG>A) polymorphism may be associated with an increased risk of HCV-related HCC development in the Pakistani population, but further validation in large, multicenter cohort studies is necessary.

Author Contribution Statement

Zaid Talal Abdulqader Ali: Study design, data collection, statistical analysis, manuscript writing. Prof. Dr. Irshad Ur-Rehman: Supervision, guidance, manuscript review. Other Authors: Assisted in data collection and logistical support.

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Funding Statement

This study was entirely self-funded by the principal investigator, with no financial support from external institutions or organizations. All authors declare no financial or personal conflicts of interest that could influence the study outcomes.

Approval and Ethical Considerations

The ethical issues in this study were addressed by obtaining approval from the Institutional Review Board (IRB) of Hayatabad Medical Complex in Peshawar, Pakistan, under reference number)1774(. All procedures were conducted in accordance with the ethical standards of the institutional and national research committee, as well as the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all participants prior to the study, ensuring their voluntary participation. The confidentiality of participants' personal data and biological samples was strictly maintained, with their use limited solely to research purposes. Additionally, all necessary measures were taken to minimize potential risks and ensure the safety of participants throughout the study, thereby upholding the highest ethical and professional standards.

Availability of Data

The raw and analyzed data that support the findings of this study are available upon reasonable request. Interested researchers may contact me for further details regarding data access.

Study Registration

This study was registered as a case-control study following research and ethical compliance guidelines.

Conflict of Interest Statement

I declare no conflict of interest in relation to this research. There are no financial, professional, or personal

factors that could have influenced the study's findings.

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