RESEARCH ARTICLE

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Association of *XRCC1* Gene Polymorphism with an Increased Risk of Hepatocellular Carcinoma in the Peshawar Population

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Abstract

Objective: This study aimed to examine the association between variations in the *XRCC1* gene and the risk of hepatocellular carcinoma in individuals from Peshawar with chronic hepatitis C infection. **Methods:** The study included three groups of participants: 30 individuals with HCC resulting from chronic HCV infection, 30 participants with HCV-related cirrhosis, and 30 healthy controls. Detailed clinical and laboratory data were collected for all participants. The ARMS-PCR (Amplification Refractory Mutation System-Polymerase Chain Reaction) method was utilized to identify a single nucleotide polymorphism (SNP) in the *XRCC1* gene. **Result:** The analysis revealed that HCC patients had a significantly higher occurrence of *XRCC1* (AA and GA) genotypes and an increased frequency of the A allele compared to both cirrhotic HCV patients and healthy controls. Additionally, individuals with the *XRCC1* (AA and GA) genotypes demonstrated greater tumor foci and larger tumor sizes. Multivariate analysis revealed that the *XRCC1* rs25487 polymorphism independently contributes to a higher likelihood of developing HCC in patients with chronic HCV, with a 2.66-fold. **Conclusion:** The polymorphism of the *XRCC1* gene is probably linked with an elevated risk of hepatocellular carcinoma in individuals with chronic HCV infection. These findings underscore the importance of genetic factors in assessing HCC risk.

Keywords: *XRCC1*- Hepatocellular carcinoma- HCV- SNP- ARMS-PCR

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Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths and the sixth most prevalent cancer worldwide [1]. According to the 2022 Global Cancer Observation (GLOBCAN) report by the World Health Organization (WHO), HCC accounted for approximately 758,725 deaths and 866,136 newly diagnosed cases worldwide. In Asia, HCC is a major health burden, contributing to 70% of global incidence and mortality rates [1]. In Pakistan, HCC is the fifth most common type of cancer, making up 4.8% of all cancer cases. The ratio of incidence between males and females is approximately 4:1, with the most common age of diagnosis ranging from 40 to 70 years. Infections with hepatitis B virus (HBV) and hepatitis C virus (HCV) are the main causes of HCC in the country, with an estimated 50 million HBV carriers and 10 million HCV carriers [2]. HCV alone is responsible for 60–70% of HCC cases in Pakistan [2, 3]. Chronic HCV infection increases oxidative stress in liver tissues by producing reactive oxygen species (ROS) and nitrogen oxide (NO), leading to cellular damage. These reactive molecules disrupt cellular components such as lipids, proteins, and DNA. The ensuing genomic instability, a hallmark of HCC, overwhelms the antioxidant defenses and DNA repair mechanisms of affected cells [4].

DNA repair mechanisms are essential for maintaining genomic stability and preventing genetic mutations. They include nucleotide excision repair (NER), mismatch repair (MMR), double-strand break repair (DSBR), single-strand break repair (SSBR), and base excision repair (BER) [5]. Among these, the BER pathway specializes in repairing single-strand breaks and small lesions, including oxidative, alkylation, and deamination damage [6]. The *XRCC1* protein, synthesized from the *XRCC1* gene found on chromosome 19 (19q13.2), is crucial for the base excision repair (BER) pathway. It serves as an essential organizer by binding with various repair enzymes, directing them to sites of damage, and boosting the efficiency of the repair process [7].

Numerous single nucleotide polymorphisms (SNPs)

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have been identified in the *XRCC1* gene. While many are synonymous, some non-synonymous SNPs significantly impact protein structure and function [8]. One such variant, *XRCC1* Arg399Gln (rs25487),results from a G-to-A substitution at position 28152 on exon 10, leading to an arginine-to-glutamine amino acid change at position 399 [9]. This alteration compromises *XRCC1* protein functionality, reducing the efficiency of BER, thereby increasing DNA damage and elevating cancer risk [10]. Multiple studies have indicated associations between *XRCC1* variants and different cancers, including gastric [11], lung [12], thyroid [13], and breast cancers [14]. This study focuses on examining the rs25487 SNP of the *XRCC1* gene as a potential risk factor for hepatocellular carcinoma in the Peshawar people. The Aim of this study was examining the rs25487 SNP of the *XRCC1* gene as a potential risk factor for hepatocellular carcinoma in the Peshawar people.

Materials and Methods

Study protocol

A case-control design was conducted at the Center of Biotechnology and Microbiology, University of Peshawar, from January to August 2024. Ninety participants took part in the study, split into three balanced groups: thirty patients diagnosed with hepatocellular carcinoma (HCC) resulting from chronic hepatitis C virus (HCV) infection, thirty individuals with post-HCV cirrhosis who showed no radiological signs of HCC, and thirty healthy controls matched for age and gender.

All appropriate assessments have been undertaken through medical history, examination of the physical body, and scanning, especially radiological ones: an abdominal ultrasound scan as well as a tri-phased computerized tomography (CT) scan. The tests assess marker levels for hepatitis B and C, and alpha-fetoprotein serum level. Exclusion criteria were patients suffering from liver cirrhosis or HCC due to chronic infections other than HCV.

Study protocol received approval from the ethics committee of the University of Peshawar. Both patients and healthy controls who participated in the study were given informed written consent prior to their participation.

Routine laboratory investigations

After collecting the clinical data, these patients were undergone a few mandatory laboratory tests. Complete blood counts were analyzed using Mindray BC-6000 series Automated Hematology Analyzer (Min-dray Bio-Medical Electronics Co., Ltd, Shenzhen, China). A15 Biochemistry Auto Analyzer of BioSystems S.A., Barcelona, Spain was used to perform liver function tests. BFT II Analyzer of Dade Behring Marburg GmbH, Germany was used to determine the concentration of prothrombin and INR. Serum AFP levels and hepatitis serology (HBsAg and HCV Ab) were determined using the Mindray CL-1200i Immuno-assay Analyzer (Mindray Bio-Medical Electronics Co., Ltd, Shenzhen, China).

DNA isolation and genotyping

Venous blood samples were collected individually in the study, and genomic DNA was prepared utilizing the TransGen Biotech DNA Purification Kit (TransGen Biotech Company, Beijing, China). The *XRCC1* rs25487 polymorphism was detected using the ARMS-PCR. ARMS-PCR is an allelic-specific PCR procedure that employs allele-specific primers for amplifying either the wild-type or mutant allele.

Primers used were

Mutant reverse: 5'–GCGTGTGAGGCCTTACCTAC–3'
Wild reverse: 5'–GCGTGTGAGGCCTTACCTAT–3'
Common forward: 5'–CACACCTAACTGGCATCTTC–3'

The PCR was performed in duplicate with each reaction mixture consisting of 0.7 µL of each primer, 10 µL of 2X TransGen Biotech Blue Master Mix, 7.1 µL of nuclease-free water, and 1.5 µL of genomic DNA, reaching a total volume of 20 µL. Amplification was carried out using the Perkin Elmer Gene Amp PCR System 2400 Thermal Cycler. The protocol began with an initial denaturation at 94°C for 5 minutes, followed by 35 cycles of denaturation at 94°C for 35 seconds, annealing at 58°C for 30 seconds, and extension at 72°C for 30 seconds. A final extension at 72°C for 5 minutes ensured complete elongation. PCR products were analyzed by 2% agarose gel electrophoresis and visualized under a UV transilluminator. A DNA ladder was used as a size marker as in Figure 1, and a negative control without DNA was included to confirm the absence of contamination. This approach helped validate the specificity and reliability of the amplification for further applications.

Result Interpretation

• Single band at position of mutant allele- homozygous mutant genotype (AA).

• A single band at the wild-type allele position indicates homozygous normal genotype (GG).

• The presence of bands both at positions, this is indicating a heterozygous genotype (GA).

Statistical analysis

The data were structured and analyzed with SPSS software version 25 (IBM Corporation, Armonk, NY. Descriptive statistics such as means and standard deviations were utilized. Analytical tests used include the Chi-square test, Mann-Whitney U test, Kruskal-Wallis test, ANOVA with Dunn's post-hoc test, Fisher's Exact test, and Odds Ratio (OR) calculations along with Confidence Intervals (CI). A p-value < 0.05 was considered significant.

Results

Demographic Overview of Participants

Age and gender profiles of the three groups showed no marked differences, as reflected in (Table 1). However, it can be observed from (Table 2) that there are marked differences in the three groups as far as platelet counts, liver function tests, and AFP are concerned. It has been seen that as compared to the cirrhotic group, HCC patients show higher values of ALT, alkaline phosphatase, direct bilirubin, and AFP, but the albumin value was less. There

Table 1. Demographic Characteristics of the Studied Groups

	Group I (HCC) (n=30)	Group II (Hepatitis C) (n=30)	Group III (Control) (n=30)	Test of significance	P-value
Gender					
Male	21	18	20	0.689	0.709
Female	9	12	10		
Age (Years)					
Range	45 – 82	40 – 80	40 – 83	F = 1.49	0.091
SD ± Mean	9.19 ± 62.2	12.09 ± 55.86	13.29 ± 54.10		
Median	63	56.5	48		

χ^2; p, χ^2 and p values for the Chi-square test for comparing between the three studied groups; F; p, F, and p values for the ANOVA test

were no notable differences observed between groups in platelet count, INR, AST, total bilirubin, or alkaline phosphatase.

Frequency of XRCC1 Genotypes and Alleles in the Population Groups

The distribution of *XRCC1* (rs25487) genotypes and alleles among groups is illustrated in Figures 1 and 2 and Table 3. The control group had a significantly increased frequency of the GG genotype as compared to the HCC group (73.4% vs. 23.3%, p < 0.001), and also had a decreased frequency of the A allele (20.6% vs. 57.5%, p = 0.002). The HCC group showed a significantly higher frequency of AA and GA genotypes (76.7%) as compared to both healthy controls (26.6%, p < 0.001) and cirrhotic patients (53.3%, p < 0.001).

Association between XRCC1 gene rs25487and Hepatocellular Carcinoma

The univariate analysis indicates that the risk for HCC was found to be 2.875 times higher with the AA and GA genotypes in comparison to the GG genotype.

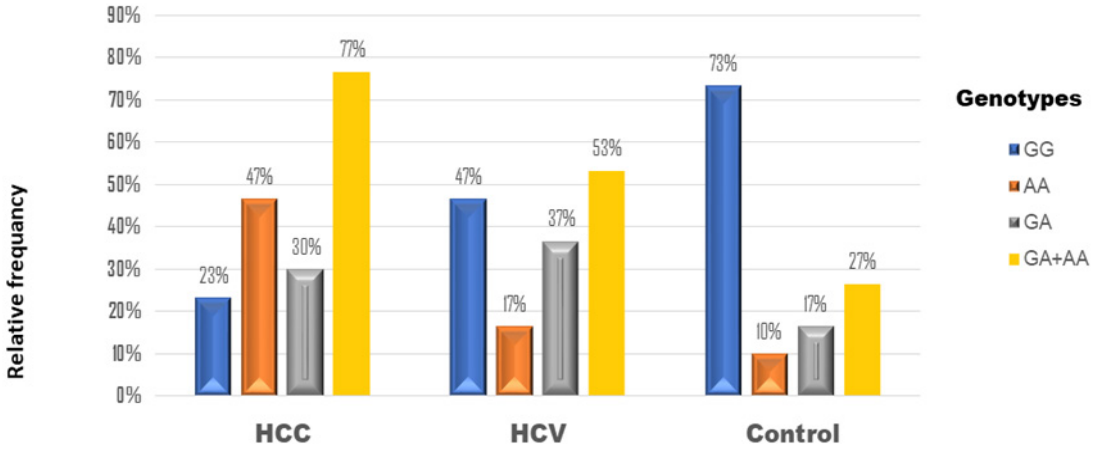

Figure 1. Illustrates the Comparison of *XRCC1* rs25487 Genotype Distribution (Genotypes GG, GA, AA, and GA+AA) among the Different Studied Groups.

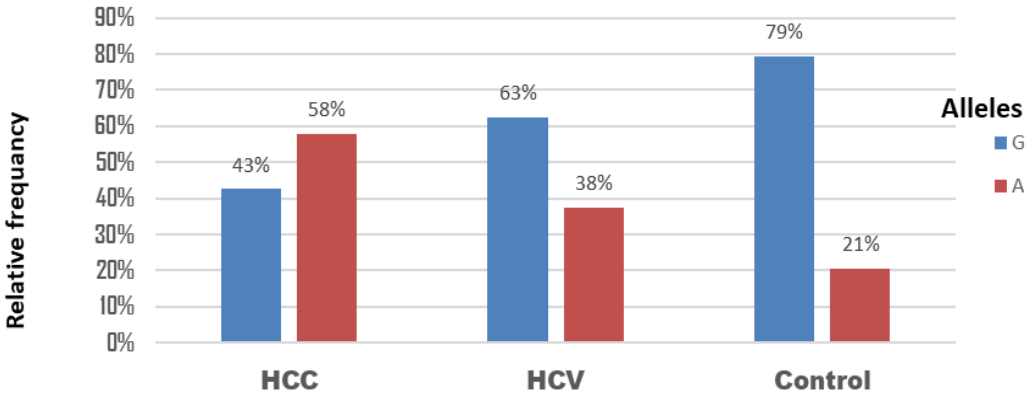

Figure 2. Illustrates the Comparison among the Different Studied Groups in Terms of the Distribution of *XRCC1* (rs25487) Allele Frequencies

Table 2. Statistical Analysis of the Laboratory Results among the Studied Groups

Laboratory parameters	Studied Groups			Test of Significance	P-value	Significance
	G-I (HCC) (n=30)	G-II (Hepatitis C) (n=30)	G-III (Control) ((n=30)			
Plts						p1=0.96*
Range	100 – 503	99 – 415	228 – 501	H = 28.4	<0.001*	p2<0.001*
Median	210	209	313.5			p3<0.001*
PT						p1=0.440*
Range	12 – 32	12 – 25	13 – 17	H = 14.26	0.001	p2<0.001*
Median	14	17.5	14			p3=0.030*
GPT						p1=0.05*
Range	8 – 417	18 – 290	6 – 32	H = 45.4	<0.001*	p2<0.001*
Median	84.5	59	18			p3<0.001*
GOT						p1=0.08*
Range	10 – 567	17 – 200	6 – 35	H = 38.3	<0.001*	p2<0.001*
Median	75	50	18			p3<0.001*
ALP						p1=0.02*
Range	108 – 626	90 – 512	45 – 201	H = 40.3	<0.001*	p2<0.001*
Median	374	230	120.5			p3<0.001*
Albumin						p1=0.01*
Range	0.8 – 5.4	1.4 – 5.0	3.9 – 5.6	F = 32.17	<0.001*	p2<0.001*
Median	3.4	3.1	4.8			p3<0.001*
Total bilirubin						p1=0.31*
Range	0.4 – 14.5	0.8 – 13.0	0.3 – 1.0	H = 33.64	<0.001*	p2<0.001*
Median	1.85	2	0.7			p3<0.001*
Direct bilirubin						p1=0.021*
Range	0.2 – 1.9	0.2 – 3.7	0.1 – 0.2	H = 46.69	<0.001*	p2<0.001*
Median	0.4	0.5	0.1			p3<0.001*
AFP						p1=0.001*
Range	782 – 22000	0.8 – 4.1	0.3 – 3.1	H = 61.9	<0.001*	p2=0.018*
Median	1742	1.95	1.15			p3<0.001*

INR, International Normalized Ratio; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; ALP, Alkaline phosphatase; AFP, alfa fetoprotein; F,p, F and p values for ANOVA test; Significance among groups was done using Post Hoc Test (LSD); H, p, H and p values for Kruskal Wallis test, Significance among groups was done using Post Hoc Test (Dunn's multiple comparisons test); *, Statistically significant at $p \leq 0.05$; p1, p value for comparing between group I and group II; p2, p-value for comparing between group I and group III; p3, p value for comparing between group II and group III

XRCC1 (rs25487) polymorphism, independent of other risk factors, was confirmed by multi-variate analysis to increase HCC risk in chronic HCV patients by 2.669-fold (Table 4).

Besides, patients with AA or GA genotypes had a significantly greater number ($p = 0.031$) and size of tumor foci ($p = 0.002$); however, no differences were found in the Child-Pugh classification ($p = 0.235$). The characteristics of focal lesions between GG and GA/AA genotypes were further analyzed, and significant differences were found in both the number and size of lesions ($p = 0.031$ and $p = 0.002$, respectively), while Child-Pugh scores were not different (Table 5).

Discussion

Hepatocellular carcinoma is a complex interaction of genetic predispositions and environmental factors that enable the cancer to progress as a malignancy of the liver [15]. Understanding these factors can help clarify the mechanisms involved in the pathogenesis of HCC and improve screening methods for people at high risk. DNA repair processes are essential for preserving genomic stability and preventing carcinogenesis. The BER plays an especially important role since it fixes DNA damage by ionizing radiation, chemical alkylating agents, and a variety of other sources such as viral infection [4]. The *XRCC1* gene is an integral part of the BER pathway. Variants in this gene linked to an enhanced risk of cancer caused by interference with the interaction of several repair proteins [5-7].

Numerous studies discuss the relationship between *XRCC1* SNPs and susceptibility to HCC. For instance, Xia et al. [16] identified some *XRCC1* variants (c.910A>G and c.1686C>G) as strongly linked to a higher HCC risk . Liu et al. [17] also deter-mined the c.1804C>A polymorphism

Table 3. Distribution of *XRCC1* (rs25487) Genotype and Allele Frequencies among the Studied Groups

	Group I (HCC) (n=30)		Group II (Hepatitis C) (n=30)		Group III(Control) (n=30)		χ^2	P - Value	Significance b/w groups
	No.	%	No.	%	No.	%			
Genotypes									
GG	7	23.3	14	46.7	22	73.4	19.4	0.001	P1=0.033*
AA	14	46.7	5	16.6	3	10			P2<0.001*
GA	9	30	11	36.7	5	16.6			P3=0.123
GG	7	23.3	14	46.7	22	73.4	15.05	0.001	P1=0.103
									P2<0.001*
AA + GA	23	76.7	16	53.3	8	26.6			P3=0.064
Alleles									P1=0.117
G	17	42.5	25	62.5	27	79.4	10.58	0.005	P2<0.002*
A	23	57.5	15	37.5	7	20.6			P3=0.133

χ2, p, χ2 and p values for Chi square test for comparing between the three groups; Significance among groups was done using Fisher Exact test; *, Statistically significant at $p \leq 0.05$; p1, p value for comparing between group I and group II; p2, p value for comparing between group I and group III; p3, p value for comparing between group II and group III

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

Variables	P-value	Odd Ratio	95% Confidence Interval	
			Lower	Upper
Age	0.0049	1.0685	1.0233	1.1237
Gender	0.418	0.6428	0.2158	1.8629
Viral load	0.086	1.003	0.988	1.004
Genotypes (AA+GA)	0.062	2.875	0.9722	9.1266
Child pugh classification(B+C)	0.078	2.242	0.567	8.541
Multivariate Analysis				
Variables	P-value	Adjusted Odd Ratio	95% Confidence Interval	
			Lower	Upper
Age	0.012	1.204	1.021	1.231
Viral load	0.127	1.001	1	1.002
Genotypes (AA+GA)	0.04992 *	2.669	1.0403	12.722
Child pugh classification(B+C)	0.204	2.131	0.654	7.562

to be another potential contributor to elevated HCC risk . Kiran et al. [18] established that the *XRCC1* genotypes Arg194Trp and Arg280His are associated with increased HCC susceptibility, especially in the presence

Table 5. Comparison of *XRCC1* Genotypes as Regard to HCC Characteristics

	GG (n=7)		GA+AA (n=23)		Test of significant	P - Value
	No.	%	No.	%		
N. Foci						
Single	5	71.4	6	26	χ^2= 4.7	0.031
Multiple	2	28.6	17	74		
Size (cm)						
Max - Min	1.5-5		3.7 - 12		U=27.30	0.002
SD ± Mean	2.72 ±1.17		5.17 ± 2.39			
Median	2.5		6.2			
Child Pugh classification						
A	2	28.5	3	13	χ^2=2.9	FEp= 0.235
B	3	43	5	21.7		
C	2	28.5	15	65.3		

χ2, p, χ2 and p values for Chi square test; FEp, p value for Fisher Exact for Chi square test; U, p, U and p values for Mann Whitney test; *, Statisti¬cally significant at $p \leq 0.05$

of Arg399Gln . Further studies by Qi et al. [19] and Bazgir et al. confirmed the *XRCC1* Arg399Gln variant and a higher HCC risk association [20]. Conversely, a meta-analysis by Liu et al. [21] in 2011 revealed that no significant relationship exists, therefore more studies should be conducted. Moreover, The *XRCC1* rs25487 variant has been linked to an elevated risk of cancer, especially for breast cancer. Researchers have determined that the AA genotype and the A allele are associated with a predisposition to disease onset [20].

This research investigated the correlation between the *XRCC1* rs25487 polymorphism and the susceptibility to HCC in HCV-infected individuals within the Peshawari population. The rs25487 SNP is characterized by a G change to A at position 28152 in exon 10, resulting in an arginine-to-glutamine substitution (Arg399Gln) [14]. The findings revealed that AA and GA genotypes were significantly more common in HCC patients (76.7%) compared to cirrhotic HCV patients (53.3%) and healthy controls (26.6%). Additionally, the A allele frequency was higher in the HCC group (57.5%). Multivariate analysis identified *XRCC1* rs25487 SNP as a potential predictor for HCC in chronic HCV patients, which increased the risk 2.66 times. Moreover, patients with AA and GA genotypes showed greater and more numerous tumor foci and more advanced Child-Pugh classifications.

These findings align with those of Qi et al. [19], who investigated the rs25487 polymorphism in a Chinese HCC population. Their study found that individuals with AA and GA genotypes had an elevated HCC risk compared to those with the GG genotype, with an odds ratio of approximately 2.5. The genotypes were also linked to advanced tumor stages and larger tumor sizes, suggesting that rs25487 influences both HCC risk and progression. Similar results were confirmed by Bazgir et al. (2018), Kiran et al. [18], and Liu et al. [21].

In conclusion, to summarize, the *XRCC1* rs25487 polymorphism may be linked to a higher risk of HCC-related HCV in the Peshawar population. However, further large-scale, multi-center studies are necessary to confirm this association.

Author Contribution Statement

Rashid Saeed Abdo Hassen: 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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General

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Approval

This study was approved by the Advanced Studies Research Committee, University of Peshawar, as part of an approved student thesis

Data Availability

The data supporting this study will be made available upon request by contacting the corresponding author via email.

Ethical Declaration

This study was conducted in accordance with the Declaration of Helsinki, ensuring compliance with ethical research standards. The research protocol received formal approval from the Ethics Committee of Hyatabad Medical Complex (Approval No. 1747) on 28/02/2024

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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