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ORIGINAL ARTICLE

Relation of XRCC1 Gene Polymorphism with Development of HCC among Patients with HCV Related Cirrhosis

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ABSTRACT

Background: Among Egyptian females, hepatocellular carcinoma (HCC) ranks sixth, while among males it ranks second. The X-ray repair cross-complementing group1 (XRCC1) could play a crucial role in reparation of oxidative DNA damage. An association was revealed between the risk of HCC and the genotypes and allele distribution of XRCC1 variants.

Objectives: This research aimed at the evaluation of the relationship between XRCC1 gene polymorphism and the development of HCC among Egyptian patients who had HCV related cirrhosis.

Patients and methods: This study recruited 93 individuals, including 31 apparently healthy subjects taken as controls (Group I), 31 cirrhotic patients with chronic hepatitis C virus (HCV) infection (Group II), and 31 HCC patients with HCV related cirrhosis (Group III). Xrcc1 gene polymorphism c.1517 G>C was determined using Polymerase Chain Reaction-Restricted Fragment Length Polymorphism (PCR-RFLP).

Results: CC genotype was significantly increased (p=0.04) among HCC patients with HCV related cirrhosis (48.4%) compared to controls (12.9%). Also, C allele was significantly higher (p=0.01) among HCC patients (59.7%) compared to both cirrhotic patients (41.9%) and controls (33.9%). HCC patients had CC genotype 5.83 times more when compared to controls (OR=5.83, 95% CI= 1.46-23.3). HCC patients had C allele 2.89 times more when compared to controls (OR= 2.89, 95% CI= 1.39-6). The frequencies of (GC+CC) genotypes when combined were higher in HCC patients (71%) compared to both cirrhotic patients (58.1%) and controls (54.8%).

Conclusion: The polymorphism of XRCC1 c.1517G>C was found to be associated with increased risk of HCC among patients with HCV related cirrhosis, besides; C allele had higher risk of HCC.

Keywords: Hepatocellular carcinoma, xrcc1 polymorphism, cirrhosis.

INTRODUCTION

Worldwide, 170 million people are infected with hepatitis C virus. Fifty to eighty percent of HCV patients will develop chronic infection, putting them at high risk for cirrhosis (20%) and hepatocellular carcinoma (HCC) [1]. Chronic hepatitis C virus (HCV) infection is a major public health problem in many low- and middle-income countries. In 2015, Egypt's HCV infection prevalence of 7% among adults was among the highest in the world and accounted for 7.6% of the country's mortality. In 2014, Egypt embarked on an aggressive screening and treatment program that evolved into a national strategy to eliminate HCV as a public health threat by 2021 [2]. If the presence of hepatitis C virus RNA in the blood continues for over six months following the beginning of acute infection, it is referred to as chronic hepatitis C. It is rare for an infection to resolve on its own when it becomes chronic. About 20% to 30% of people will develop cirrhosis within a 25- to 30-year timeframe. Hepatic

decompensation, hepatocellular cancer, and liver-related mortality are all risks that patients face as cirrhosis develops [3]. In Egypt, hepatocellular carcinoma (HCC) ranks fourth cancer, whereas worldwide, it ranks sixth [4]. When it comes to carcinogenesis in the liver, both hereditary and environmental factors play a role. DNA repair systems work together to prevent cancer by preserving genomic integrity. The main defense against exons created by ionizing radiation and powerful alkylating chemicals, as well as other DNA-damaging agents like viruses, begins with base excision repair (BER) [5]. Researchers have discovered that the XRCC1 gene is essential for the repair mechanism that occurs after base excision. It is involved in the base excision repairing pathway through its interactions with DNA ligase III, polymerase beta, and poly (ADP-ribose) polymerase [6]. XRCC1 mutations affect DNA repair ability by disrupting its interaction with other enzymatic proteins; they may increase the risk of cancer [5]. Several studies were performed in different countries for the evaluation of the relation of XRCC1 gene polymorphism and the development of HCC among patients who had HCV related cirrhosis. So, this study aimed at the evaluation of the relationship between XRCC1 gene polymorphism and the development of HCC among Egyptian patients who had HCV related cirrhosis at our single center Zagazig University Hospital.

PATIENTS AND METHODS

Study population

This case control study conducted at the Clinical Pathology and Tropical Medicine Departments, Faculty of Medicine, Zagazig University during the period from March 2023 to July 2023. Written informed consent was obtained from all participants after explaining the procedure and medical research. The research was conducted under the World Medical Association's Code of Ethics (Helsinki Declaration) for human research. This study was carried out after the approval of the Institutional Review Board (IRB) (#:6739-21-2-2021). This study included 93 participants who aged more than 18 years and they were recruited and allocated into three groups (each included 31 participants); Group I: involved 31 apparently healthy subjects with matched age and sex to the other two groups, Group II: involved 31 cirrhotic patients who had chronic HCV infection, and Group III: involved 31 HCC patients with HCV related cirrhosis. Diagnosis of Hepatitis C virus was done by detection of HCV antibodies by electro-chemiluminescence immunoassay "ECLIA' on the Cobas e 411 immunoassay analyzer (Roche, Germany). Patients with other causes of cirrhosis, with extra hepatic malignancy, less than 18 years and more than 60 years were excluded from the study. Patients were subjected to full history taking and clinical examination, radiological investigations were done for all patients as abdominal U.S. Staging for HCC patients were done according to Barcelona Clinic Liver Cancer staging (BCLC) [7].

Laboratory investigations

Venous Blood samples were collected from all participants under complete aseptic conditions. Routine laboratory investigations were performed including complete blood count (CBC), Liver and kidney function tests, alpha fetoprotein (AFP), and Coagulation profile. Two ml of venous blood under complete a septic condition was delivered to EDTA tube for detection of XRCC1 gene polymorphism c.1517 G>C using Polymerase Chain Reaction-Restricted Fragment Length Polymorphism (PCR-RFLP)

Detection of XRCC1 gene polymorphism by (PCR-RFLP):

Extraction of genomic DNA from peripheral blood by Genomic DNA mini kits for DNA Extraction (Geneaid, USA): After the elution, DNA concentration was measured using the QUANTUS TM FLUOMETER (Promega, USA). Amplification of the extracted DNA for detection XRCC1 polymorphism using MyTaq™ Red Mix (enzynomics, England): Primers used in the PCR reaction were;

Forward primer (5'-CAAGTCCCAGCTGAGAACTGAG-3')

Reverse primer (5' GCTGCTCTGCATGCTCACTC -3')

PCR reactions were performed in a total volume of (20µl); Ready-to-use PCR master mix (10µl), reverse primer (1 µl), forward primer (1 µl), genomic extracted DNA (8µl).

The reaction mixture was placed inside the heating block in the DNA thermal cycler then subjected to the following conditions; first denaturation for 5 minutes at 94°C, then 35 PCR cycles, each cycle consisted of: denaturation at 94°C for 35 seconds, annealing at 59°C for 35 seconds and extension at 72°C for 35 seconds, then final extension at 72°C for 5 minutes.

Restriction analysis of the PCR amplified product by the restriction enzyme HAEIII (enzynomics ,

England) for detection of mutation in xrcc1 gene c.1517G>C was done according to the following reaction mixture ; (total volume = 10uL) ; nuclease-free water (3µL), 10X NE Buffer (1 µL),amplified PCR product(5 µL) and HaeIII enzyme (1 µL). All components were mixed gently and spin down and incubated at 37°C for one hour. Digested PCR fragments were separated by electrophoresis on 2% agarose gel.

The results were interpreted as one uncut fragment of 247 bp was for the wild type allele (GG), two fragments of 168 bp and 79 bp was for mutant homozygous allele (CC) and three fragments of 247 bp, 168 bp and 79 bp was for the heterozygote allele (GC) (Figure 1).

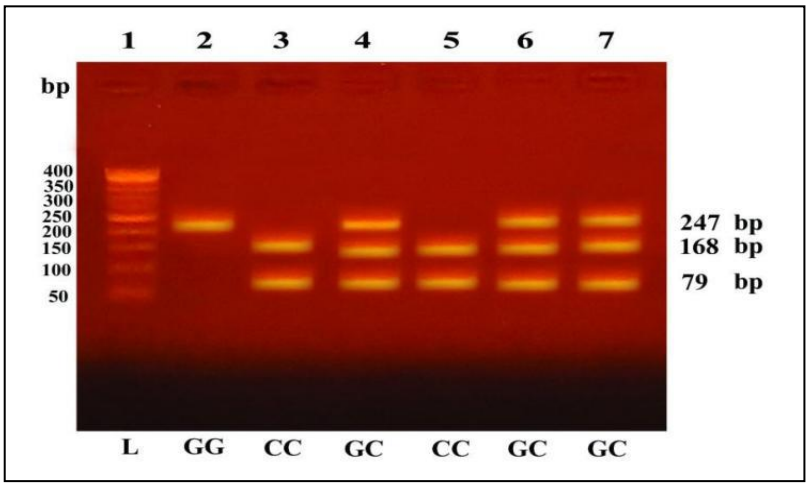

Figure (1): Agarose gel electrophoresis of PCR fragments digested by HaeIII restriction enzyme.

Statistical analysis:

We used SPSS 27.0 (IBM, 2020) to do statistical analyses on the data we gathered. Frequencies and relative percentages were used to represent the qualitative data. To determine the difference between the qualitative variables, a chi-square test was employed. Data that could be quantified were presented as means plus or minus standard deviations. When dealing with normally distributed data, we utilized an independent T test to determine the difference between the two groups' quantitative variables. When there were more than two groups of normally distributed quantitative variables, the ANOVA F-test was employed to determine the difference. To determine the difference between quantitative variables in more than two groups with non-normally distributed data, the Kruskal Wallis test was employed.

RESULTS

This study was conducted on 93 individuals including 31 apparently healthy subjects as controls they matched well with patients as regard age and sex, they were 19 males (61.3%) and 12 females (38.7%) with their ages ranged from (22 -51 years), 31 cirrhotic patients with chronic HCV infection, they were 19 males (61.3%) and 12 females (38.7%) with their ages ranged from (24–57years) and 31 HCC patients with HCV related cirrhosis , they were 20 males (64.5%) and 11 females (35.5%) with their ages ranged from (22 – 60) years. High statistical significant increase was found in total and direct bilirubin, alanine transaminase (ALT), aspartate aminotransferase (AST), international normalized ratio (INR), AFP and decrease in albumin, hemoglobin (Hb), platelets and white blood cells (WBCs) among HCC patients with HCV related cirrhosis compared to both cirrhotic patients and controls ($p<0.001$). Moreover, highly statistically significant increase was found in total and direct bilirubin, ALT, AST, and AFP among cirrhotic patients when compared to controls ($p<0.001$). Besides, statistically significant increase was found in creatinine among HCC patients compared to controls ($p=0.03$) (Table 1).

Table 1 : Laboratory findings among the studied groups.

Variable		Group I (*n*=31)	Group II (*n*=31)	Group III (*n*=31)	Test	P	Post hoc
T.bilirubin (mg/dl)	*Median Range*	0.5 0.13-1.1	0.8 0.26-6.6	3.4 0.78-9.05	**KW 52.42**	**<0.001 ****	**0.002*[1] <0.001**[2] <0.001**[3]**
D.bilirubin (mg/dl)	*Median Range*	0.20 0.08-0.9	0.3 0.1-5.9	2.13 0.18-5.41	**KW 47.02**	**<0.001 ****	**0.02*[1] <0.001**[2] <0.001**[3]**
S.Albumin (gm/dl)	*Mean ± SD Range*	3.42±0.57 2.2-4.63	3.43±0.77 2-4.8	2.54±0.6 1.5-4.06	**F 19.03**	**<0.001* ***	0.99 NS[1] **<0.001**[2] <0.001**[3]**
SGOT (U/L)	*Median Range*	19 11.4-32	33.8 15-345	165 26.2-496	**KW 63.67**	**<0.001 ****	**<0.001**[1] <0.001**[2] <0.001**[3]**
SGPT (U/L)	*Median Range*	19 11.2-37	30.1 16.5-412	501 51.4-1110	**KW 66.19**	**<0.001 ****	**<0.001**[1] <0.001**[2] <0.001**[3]**
INR	*Mean ± SD Range*	1.17±0.17 1-1.7	1.25±0.35 1-276	2.06±0.63 1.1-3.74	F 41.03	**<0.001 ****	0.73 NS[1] **<0.001**[2] <0.001**[3]**
AFP (ng/dl)	*Median Range*	7.3 2.2-36.9	16.9 2.8-1854	881 137-2945	**KW 59.89**	**<0.001 ****	**0.003*[1] <0.001**[2] <0.001**[3]**
Hb:(gm/dl)	*Mean ± SD Range*	13.87±1.28 11.9-16.1	12.99±1.59 10.4-16	9.6±1.82 6.4-12.8	**F 63.41**	**<0.001* ***	0.08 NS[1] **<0.001**[2] <0.001**[3]**
Platelets: ($x10^3/mm^3$)	*Median Range*	279 173-426	194 102-371	106 48-248	**KW 51.14**	**<0.001 ****	**<0.001**[1] <0.001**[2] <0.001**[3]**
WBCs: ($x10^3/mm^3$)	*Median Range*	7.3 3.8-10.10	7.2 2.4-13.7	4 1.95-15.4	**KW 9.70**	**0.008**	0.38 NS[1] **0.003*[2] 0.02*[3]**
Creatinine: (mg/dl)	*Mean ± SD Range*	0.83±0.23 0.4-1.2	0.90±0.22 0.5-1.4	0.98±0.20 0.6-1.3	**F 3.64**	**0.03***	0.42 NS[1] **0.02*[2]** 0.33 NS[3]

SD: Stander deviation, F: ANOVA test, KW: Kruskal Wallis test P1: Group I versus Group II P2: Group I versus Group III P3: Group II versus Group III .NS: Non significant (P>0.05) *: Significant (P<0.05) **: highly significant (P<0.001)

T.Bilirubin: Total Bilirubin, D.Bilirubin: Direct Bilirubin, S.Albumin: Serum Albumin, SGOT: Serum Glutamic Oxaloacetic Transaminase, SGPT: Serum Glutamic Pyruvic Transaminase, INR: International Normalised Ratio, AFP: Alpha Fetoprotein, Hb: Hemoglobin, WBCs: White Blood Cells

Xrcc1gene polymorphism

A significant increase (p=0.01) of CC genotype among HCC patients with HCV related cirrhosis (48.4%) compared to controls (12.9%). Moreover, The CC genotype in HCC patients with HCV related cirrhosis was higher than cirrhotic patients (25.8%). GC genotype was higher in control group (41.9%) compared to HCC patients (22.6%). GG genotype was statistically higher in control group (45.2%) when compared to HCC patients (29%) (Table 2).

Table (2): XRCC1 gene polymorphism among the studied groups.

Variable		Group I (*n*=31)		Group II (*n*=31)		Group III (*n*=31)		χ^2	P	Within groups
		No	%	No	%	No	%			
XRCC1:	*GG*	14	45.2	13	41.9	9	29	**9.68**	**0.04***	0.41 NS[1]
	GC	13	41.9	10	32.3	7	22.6			**0.01*[2]**
	CC	4	12.9	8	25.8	15	48.4			0.18 NS[3]
Allele:	*G*	41	66.1	36	58.1	25	40.3	**8.73**	**0.01***	0.35 NS[1]
	C	21	33.9	26	41.9	37	59.7			**0.004*[2]**
										0.04*[3]

χ^2: Chi square test. P1: Group I versus Group II P2: Group I versus Group III P3: Group II versus Group III , XRCC: X-ray Cross-Complementing,

Genotype frequency

Group III had CC genotype 5.83 times more when compared to controls (OR=5.83, 95% CI=1.46-23.3, p=0.009) (Table 3).

Table (3): Risk of XRCC1 gene polymorphism (Group III versus Group I).

Variable		Group I (*n*=31)		Group III (*n*=31)		χ^2	P	OR (95%CI)
		No	%	No	%			
XRCC1:	*GG*	14	45.2	9	29	--	--	1
	GC	13	41.9	7	22.6	0.08	0.78 NS	1.19 (0.34-4.14)
	CC	4	12.9	15	48.4	**6.74**	**0.009***	**5.83 (1.46-23.3)**
Allele:	*G*	41	66.1	25	40.3	**8.29**	**0.004***	**2.89 (1.39-6)**
	C	21	33.9	37	59.7			

XRCC1: X-ray Cross-Complementing, OR: Odd ratio

The frequencies of (GC+CC) genotypes when combined were higher in Group III (71%) compared to both Group II (58.1%) and Group I (54.8%) (Table 4, Figure 2).

Table (4): Risk of XRCC1 gene polymorphisms, genotype GG *vs* combined (GC&CC) among the studied groups.

Variable		Group I (n=31)		Group II (n=31)		χ2	P	OR (95%CI)
		No	%	No	%			
XRCC1:	GG	14	45.2	13	41.9	0.07	0.80	1.14(0.42-
	GC&CC	17	54.8	18	58.1		NS	3.11)
XRCC1:	GG	14	45.2	9	29	1.73	0.19	2.01(0.70-
	GC&CC	17	54.8	22	71		NS	5.75)
XRCC1:	GG	13	41.9	9	29	1.13	0.29	1.77 (0.62-
	GC&CC	18	58.1	22	71		NS	5.06)
XRCC1:	GG	14	45.2	22	35.5	0.82	0.37	1.5 (0.62-3.6)
	GC&CC	17	54.8	40	64.5		NS	

χ2: Chi square test. NS: Non significant (P>0.05)

XRCC1: X-ray Cross-Complementing, OR: odd ratio

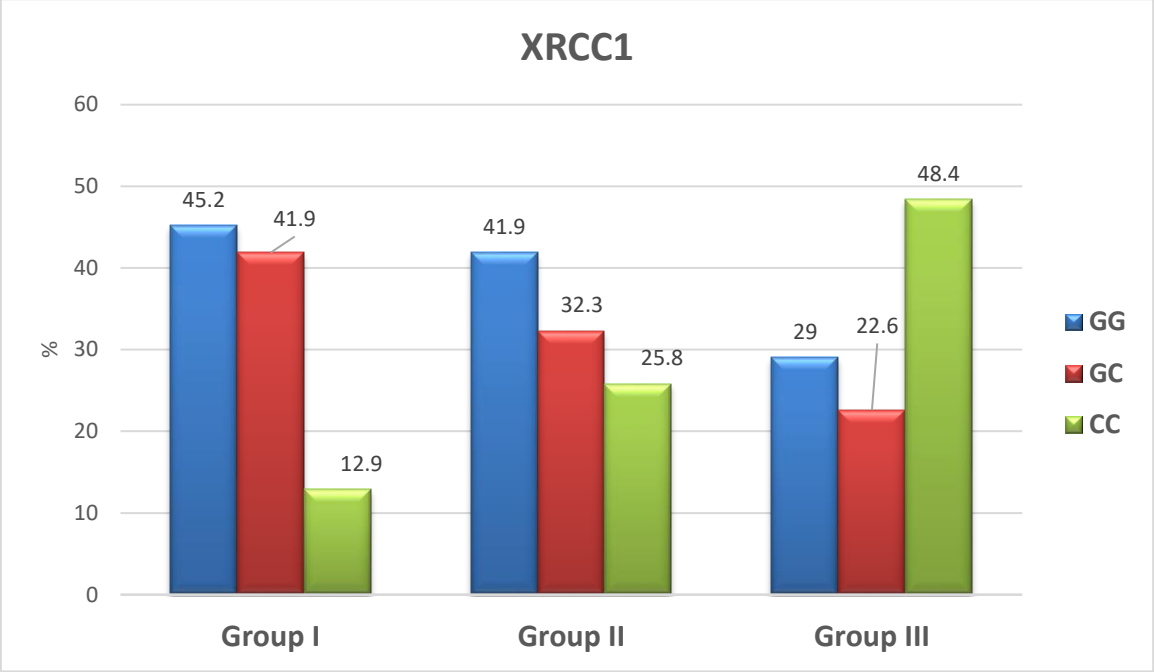

Figure (2): XRCC1 gene polymorphism among the studied groups.

Allele frequency

The C allele was significantly higher (p=0.01) among Group III (59.7%) compared to both Group II (41.9%) and Group I (33.9%) (Table 2). Group III had C allele 2.89 times more when compared to controls (OR= 2.89, 95% Confidence Interval (CI) = 1.39-6, p= 0.004**) (**Table 3).

DISCUSSION

One of the most pressing global health concerns, liver cancer ranks as the third leading cause of cancer related mortality. Worldwide, it is the sixth cancer overall, affecting all of the patient quality of life, relatives' overload and more cost on the health systems [8]. Chronic hepatitis B and C virus (HBV and HCV, respectively) infections are among of many identified risk factors [9]. DNA damage processing and genomic integrity conservation are the primary goals of DNA repair systems [10].

XRCC1 is a crucial gene that plays a role in repairing DNA damage. Certain genetic variations in XRCC1 have been linked to cancer. The XRCC1 genetic variation c.1517G>C has been linked to pancreatic cancer [5]. An association was revealed between HCC and XRCC1 gene polymorphisms, as Xia et al. [11] reported a relationship between the risk of HCC and the genotypes and allele distribution of the XRCC1 variants c.910A>G and c.1686C>G, moreover, according to Liu et al. [12], the XRCC1 genetic polymorphism c.1804C>A may be linked to an increased risk of HCC.

So, this research aimed for evaluation of the relationship between XRCC1 gene polymorphism and the development of HCC among Egyptian patients who had HCV related cirrhosis at our single centre, Zagazig University Hospital.

The current study revealed a highly statistically significant increase in total and direct bilirubin, ALT, AST, INR, AFP and decrease in albumin, Hb, platelets and WBCs among patients with HCC secondary to cirrhosis caused by chronic HCV infection compared to both cirrhotic patients and controls ($p<0.001$). Moreover, a highly statistically significant increase was found in total and direct bilirubin, ALT, AST, and AFP among cirrhotic patients when compared to controls ($p<0.001$). Besides, a statistically significant increase was found in creatinine among patients with HCC secondary to cirrhosis caused by chronic HCV infection compared to controls ($p=0.03$). There is statistically significant difference in HCC cohort than cirrhotic group regarding ALP, GGT, direct bilirubin, albumin, total protein, INR, hemoglobin, platelets count, WBCs count, jaundice, child score and classification in addition to AFP level. These results agree with previous findings of Carr and Guerra [13], Omar et al. [14], El-Hawawshy et al. [15], and Sharaf et al. [16]. On the other hand, Arafa et al. [17] showed no statistically

significant difference regarding INR, alanine aminotransferase (ALT), total bilirubin and direct bilirubin (p>0.05), this discrepancy could be due to different samples size.

The current study showed a significant increase (p=0.01) of CC genotype among HCC patients with HCV related cirrhosis (48.4%) compared to controls (12.9%). Also, C allele was significantly higher (p=0.01) among HCC patients with HCV related cirrhosis (59.7%) compared to both cirrhotic (41.9%) and controls (33.9%). As regard GC genotype, it was (22.6%) in HCC patients with HCV related cirrhosis, (32.3%) in cirrhotic cases and (41.9%) in control. GG genotype was (29%) in HCC patients with HCV related cirrhosis, (41.9%) in cirrhotic cases and (45.2%) in control. Group III had CC genotype 5.83 times more when compared to controls (OR=5.83, 95% CI=1.46-23.3, p=0.009).

Also, we revealed that frequency of combined (GC+CC) genotypes were greater in HCC patients with HCV related cirrhosis (71%) compared to cirrhotic patients (58.1%) and control group (54.8%). These results were in agreement with Naguib et al. [5] who found that CC genotype was significantly higher in HCC patients (57.5%) when compared to cirrhotic (20%) and controls (15%). Furthermore, they revealed that GC genotype was (25%) in HCC cases, (35%) in cirrhotic cases and (25%) in controls. Moreover, GG genotype was (17.5%) in HCC cases, (45%) in cirrhotic cases and (60%) in controls. Additionally, when it comes to (GC+CC) genotypes their results agreed with our results as frequency of (GC+CC) genotypes were higher in HCC patients (82.5%) when compared to cirrhotic patients (55%) and (40%) in control. In accordance with our results Bi et al. [18] found that combined (GC+CC) genotypes were (62.2%) in HCC cases which was higher than control (50.1%) . They concluded that the CC genotype was associated with a higher risk of developing HCC when compared to the GG and GC genotypes.

As regard C allele in this study there was a statistically significant increase in C allele among HCC patients with HCV related cirrhosis (59.7%) compared to both control (33.9%) and cirrhotic patients (41.9%). The C allele were 2.89 times more in HCC patients with HCV related cirrhosis when compared to control with odd ratio (OR) of 2.89, 95% Confidence Interval (CI) of 1.39-6, p value of 0.004. These results were in accordance with Naguib et al. [5] who revealed that C allele were statistically higher in HCC patients (70%) versus (37.5%) in cirrhotic patients and (25.5%) in control. Similarly Bi et al. [18] found that C allele showed higher frequency in HCC patients (38.7%) when compared to control (30.3%).

The study's strengths include being one of the updated studies to investigate the relation of XRCC1 gene polymorphism and the development of HCC among Egyptian patients who had HCV related cirrhosis. It's a case control study with accurate selectivity of cases, and their samples were collected and stored carefully according to the proper conditions.

Limitations of this study include a relatively small sample size (total of 93 subjects) and it was done in single centre so generalization of our findings need larger sample size and multicentre studies; and a few similar studies to give us more information.

CONCLUSION

From our data we concluded that the polymorphism of XRCC1 c.1517G>C was found to be associated with increased risk of HCC among cirrhotic patients secondary to HCV infection, besides; C allele had higher risk of HCC.

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