ORIGINAL ARTICLE

Possible Role of Duffy Antigen Receptor for Chemokines (DARC) Variants on Liver Fibrosis Progression in Chronic Hepatitis Patients

[1]Mona M. Hassouna, [1]Maha M. Allam, [2]Mai Abozeid*, [3]Shereen M. Neweer, [1]Mary A. Naguib

[1]Clinical and Chemical Pathology Department, National Liver Institute, Menoufia University, Shebin El-Kom, Menoufia, Egypt

[2]Hepatology and Gastroenterology Department, National Liver Institute, Menoufia University, Shebin El-Kom, Menoufia, Egypt

[3]Master's Degree in clinical Pathology, Menoufia University, Shebin El-Kom, Menoufia, Egypt

Key words:
DARC; chemokines; liver fibrosis; chronic hepatitis

Corresponding Author:
Mai Abozeid, MD
Address: National Liver Institute, Menoufia University, Shebin El-Kom, 32511, Egypt.
Tel.: +201008104356
mai.abozaid@liver.menofia.edu.eg
ORCID: https://orcid.org/0000-0003-1808-7928

ABSTRACT

Background: *Cirrhosis results from chronic liver injury. Chemokines have a central role in modulating immune activity. The Duffy Antigen Receptor for Chemokines (DARC), functioning as a decoy receptor, helps maintain chemokine balance in the bloodstream.* ***Objective:*** *To explore how the DARC rs12075 (125A > G; Asp42Gly) genetic variation relates to liver fibrosis progression in chronic hepatitis patients.* ***Methodology:*** *A case-control design was employed. The study included 80 patients with chronic hepatitis C or B (40 with cirrhosis, 40 without) and 40 matched healthy individuals as controls. All participants underwent routine diagnostic procedures and liver fibrosis assessment via FibroScan. The rs12075 polymorphism was genotyped using real-time PCR.* ***Results:*** *The GG genotype was less frequent in the cirrhotic group compared to other groups. Furthermore, a lower frequency of liver cirrhosis was observed in the dominant genetic model (GG+AG versus AA genotypes). The G allele was notably underrepresented among cirrhotic patients (25%) compared to both non-cirrhotics (40%) and controls (41.3%), showing a potential protective association (ORs of 0.5 and 0.47, p = 0.043 and p = 0.029, respectively).* ***Conclusion:*** *The DARC rs12075 polymorphism may influence fibrosis advancement in chronic viral hepatitis. The G allele potentially offers a protective effect against cirrhosis.*

INTRODUCTION

Cirrhosis is a major cause of illness and stands as the leading contributor to mortality among individuals with chronic liver disorders[1,2]. Liver fibrosis, which results from prolonged liver inflammation, typically arises from chronic hepatitis infections and is driven by disrupted wound-healing processes[3]. Despite the availability of effective antiviral therapies, chronic hepatitis B and C remain key factors in the development of liver fibrosis and its progression to cirrhosis[4]. However, fibrosis progression does not occur uniformly among all patients, suggesting that individual genetic factors may influence disease outcomes[5]. Accordingly, genetic studies affecting fibrosis progression could help in early detection of high-risk patients and could direct future therapies.

Chemokines, via classical G protein-coupled receptors, have a large impact on orchestrating the immune response following tissue injury[6]. Furthermore, chemokines have a great propensity for binding to atypical chemokine receptors (ACKRs). One such receptor, DARC, also known as ACKR1, is a non-signaling receptor that serves as a crucial regulator that interacts with chemokines implicated in inflammatory reactions[7].

DARC regulates the serum concentration of chemokines and plays many pathophysiological roles depending on its cellular expression site. It is expressed on erythrocytes and endothelial cells, including hepatic sinusoidal endothelial cells[8]. On the erythrocyte surface, it scavenges chemokines, reducing the levels of circulating inflammatory chemokines[9]. While, in the hepatic and other endothelial cells, it can transcytose chemokines, leading to chemokine immobilization and presentation to blood leukocytes[10].

The DARC gene resides on chromosome 1 (1.q22-1.q23). A nonsynonymous polymorphism, rs12075 (125A > G; Asp42Gly), has been identified as a key modulator of serum levels of monocyte chemoattractant protein-1 (CCL2) that strongly correlates with liver fibrosis[11,12]. Limited studies have explored the potential role of DARC polymorphisms in viral hepatitis. While some associations have been suggested, more research is needed[13]. Thus, we studied the possible role of DARC

rs12075 polymorphism in the progression of fibrosis in chronic hepatitis patients.

METHODOLOGY

This case-control study involved 120 participants. Among them, 80 were patients diagnosed with chronic hepatitis recruited from the Hepatology and Gastroenterology Department at the National Liver Institute Hospital, Menoufia University. Based on clinical and imaging findings, these patients were categorized into two groups: 40 with liver cirrhosis and 40 without. An additional 40 healthy individuals, matched by age and sex, were enrolled as a control group. These controls were unrelated to the patients and were selected from volunteers registered at the hospital's Blood Donation Unit. Patients who have hepatocellular carcinoma, cholangiocarcinoma, or other tumors, and also patients with concomitant HIV, were excluded.

The study procedures complied with the Declaration of Helsinki's ethical standards and received ethical clearance from the Institutional Review Board of the National Liver Institute, Menoufia University (protocol number 00578/2024). Before participating in the study, all enrolled participants signed an informed consent form.

Each subject underwent a comprehensive clinical assessment, including medical history, physical examination, abdominal ultrasound, and laboratory testing. Liver function tests, blood glucose, anti-HCV, hepatitis B surface antigen (HBsAg), and anti-HB core IgG (anti-HBc IgG) were analyzed using the Cobas 6000 analyzer (Roche Diagnostics, Germany). Coagulation parameters, including prothrombin time (PT) and international normalized ratio (INR), were assessed using the BFT II coagulometer (Siemens, Germany). Complete blood counts were determined with the Sysmex XN-1000 hematology analyzer (Sysmex Corporation, Japan).

Assessment of liver fibrosis and cirrhosis

To estimate the degree of liver fibrosis, several non-invasive tools were employed. The FIB-4 index and the aspartate aminotransferase (AST) to platelet ratio index (APRI) score were calculated[14]. Liver stiffness was measured by transient elastography using FibroScan® (Echosens, Paris)[15]. The commonly used cut-off for liver cirrhosis (F4 > 12.5 kPa) was defined for diagnosis of cirrhosis[16]. The Child-Pugh-Turcotte score was applied to further classify the severity of cirrhosis[17].

Studying ACKR1 (DARC) single nucleotide polymorphism (rs12075)

Genomic DNA was extracted from EDTA-anticoagulated whole blood samples applying the QIAamp DNA Blood Micro Kit (Qiagen, Germany). The rs12075 variant in the DARC gene (ACKR1) was genotyped by real-time PCR using a TaqMan® SNP Genotyping Assay (C_2493442_20, Catalog number 4351379, Applied Biosystems, USA) on the Qiagen Rotor-Gene Q system (Qiagen GmbH, Hilden, Germany).

PCR reactions were performed in 20 µL volumes, comprising 5 µL of DNA template, 0.5 µL of TaqMan assay mix, 10 µL of universal master mix, and 4.5 µL of nuclease-free water. To distinguish genotypes, fluorescent allele-specific probes (VIC for G allele and FAM for A allele) were used:

GATTCCTTCCCAGATGGAGACTATG[**G/A**]TG CCAACCTGGAAGCAGCTGCCCCC **(Fig. 1).**

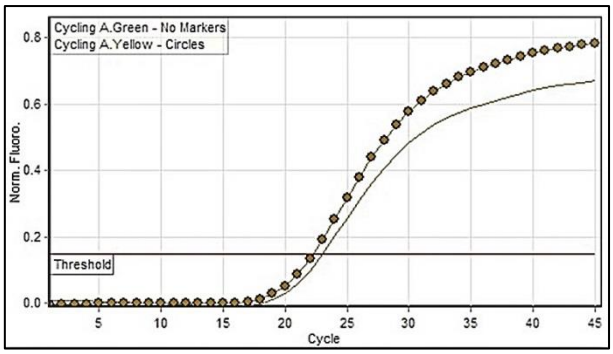

Fig. 1: Allelic discrimination for DARC rs 12057. Heterozygous AG genotype:sample showed reaction at yellow and green channels (VIC dye for G allele and FAM dye for A allele).

Thermal cycling conditions included an initial denaturation at 95°C for 10 minutes, followed by 40 cycles of 95°C for 15 seconds and 60°C for 1 second, with a final extension at 60°C for 5 minutes. Negative controls lacking DNA were included to verify the absence of contamination**.**

Statistical tests

The SPSS version 22.0 (IBM, Chicago, IL) was utilized for statistical testing. Student's t-test or ANOVA was used for comparing parametric data, while Mann-Whitney and Kruskal-Wallis tests were used for non-parametric data. Categorical variable comparisons were performed using Pearson's chi-square or Fisher's exact test, as appropriate. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to estimate risk. P-values of less than 0.05 indicate significance.

RESULTS

This study included 80 chronic liver disease patients: 40 cirrhotic patients staged F4 at fibroscan (≥ 12.5 kPa), and 40 non-cirrhotic patients staged F0-F3 at fibroscan (≤ 12.4 kPa). Cirrhotic patients exhibited significantly elevated FIB-4 and APRI scores compared to the non-cirrhotic group ($p < 0.001$). **Table 1** shows the clinical and laboratory parameters of the studied groups.

Table 1: Demographic and clinical Characteristics of cirrhotic and non-cirrhotic patients and healthy controls

Characteristics *	**Cirrhotic (GI, n= 40)**	**Non-cirrhotic (GII, n= 40)**	**Healthy controls (GIII, n= 40)**	**P-value**
Age (years), mean ± SD	56.30 ± 7.54	54.43 ± 7.14	53.70 ± 6.11	0.23 NS, 1
Gender (male), [n (%)]	22 (55.0)	21 (52.5)	22 (55.0)	0.823 NS, 2
ALT (U/L)	61.50 (35.75) a	57.50 (19.75) a	22.50 (12.75) b	**<0.001** HS, 3
AST (U/L)	50.50 (32.75) a	47.00 (16.75) a	21.00 (9.00) b	**<0.001** HS, 3
GGT (U/L)	84.00 (37.50) a	25.00 (7.75) b	19.50 (8.75) c	**<0.001** HS, 3
Total bilirubin (mg/dL)	2.85 (3.52) a	0.76 (0.25) b	0.44 (0.14) c	**<0.001** HS, 3
Direct bilirubin (mg/dL)	1.66 (1.98) a	0.25 (0.07) b	0.13 (0.07) c	**<0.001** HS, 3
Albumin (g/dL)	2.72 (0.56) a	3.75 (0.51) b	4.47 (0.59) c	**<0.001** HS, 3
INR	1.67 (0.53) a	1.07 (0.14) b	1.01 (0.14) c	**<0.001** HS, 3
Blood glucose (mg/dL)	102.00 (34.00)	96.50 (20.50)	97.00 (14.75)	0.321 NS, 3
Hemoglobin (g/dL)	11.00 (1.55) a	12.65 (1.95) b	13.45 (1.35) c	**<0.001** HS, 3
WBCs (10^3 cell/µL)	3.75 (0.90) a	7.05 (3.05) b	7.25 (2.68) b	**<0.001** HS, 3
Platelets (10^3 cell/µL)	95.00 (52.25) a	198.50 (66.50) b	276.50 (48.75) c	**<0.001** HS, 3
HBV / HCV [n (%)]	22 (55.0)/ 18 (45.0)	20 (50.0)/ 20 (50.0)	-	0.654 NS, 2
LSM (kPa)	20.20 (10.90)	7.10 (4.83)		**<0.001** HS, 4
Fibrosis stages [n (%)]				-
F0-F1 (<7.1 kPa)	-	20 (50.0)		
F2 (7.1–9.4 kPa)	-	11 (27.5)		
F3 (9.5–12.4 kPa)	-	9 (22.5)		
F4 (≥ 12.5 kPa)	40 (100.0)	-		
FIB-4 score	3.92 (2.40)	1.70 (1.14)		**<0.001** HS, 4
APRI score	1.28 (1.09)	0.56 (0.44)		**<0.001** HS, 4
Child score, mean ± SD	9.38 ± 1.94			-
Child classification [n (%)]				-
A	3 (7.5)			
B	16 (40.0)			
C	21 (52.5)			
Ascites [n (%)]				**<0.001** HS, 5
None	10 (25.0)	40 (100.0)		
Mild	15 (37.5)	0 (0.0)		
Moderate	13 (32.5)	0 (0.0)		
Marked	2 (5.0)	0 (0.0)		

*Values are expressed as median (interquartile range) unless otherwise indicated
1: ANOVA test 2: Pearson's chi square test 3: Kruskal-Wallis test
4: Mann-Whitney test 5: Fisher's Exact test
The values for the same parameter not sharing the same subscript letter are significantly different after adjustment for multiple comparisons by post hoc test at the level of 0.05
NS: Non significant at P-value ≥ 0.05 HS : Highly significant at P-value < 0.01

ACKR1 (DARC) polymorphism (rs12075) could affect progression to cirrhosis

On studying genotype and allele distribution, we noticed that the GG variant was markedly less common among cirrhotic individuals (7.5%) than among healthy controls (17.5%). In the dominant genetic model (GG + AG vs. AA), an odds ratio (OR) of 0.4 [95% CI: 0.16–0.98, p = 0.044] was observed. The G allele frequency in cirrhotic patients was 25%, significantly lower than in both the control group (41.3%) and non-cirrhotic group (40%), yielding ORs of 0.47 (p = 0.029) and 0.5 (p = 0.043), respectively. However, when comparing non-cirrhotic patients to healthy controls, no significant differences in genotype or allele frequencies were noted. Additionally, while the dominant model approached significance when comparing cirrhotics to non-cirrhotics, the p-value (0.073) did not reach the conventional threshold **(Table 2).**

Table 2: Genotypes distribution and allele frequencies of DARC rs12075 SNP in cirrhotic and non-cirrhotic patients and healthy controls groups

DARC rs12075 SNP	Cirrhotic	Non-cirrhotic	Healthy controls	P value	Cirrhotic vs. healthy controls		Non-cirrhotic vs. healthy controls		Cirrhotic vs. non-cirrhotic	
	n= 40	n= 40	n= 40		OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Genotypes				0.239 NS, a						
GG (var)	3 (7.5)	7 (17.5)	7 (17.5)		0.26 (0.06 -1.18)	0.086 NS, b	0.93 (0.26 -3.34)	0.916 NS, a	0.28 (0.06 -1.25)	0.152 NS,b
AG	14 (35.0)	18 (45.0)	19 (47.5)		0.45 (0.17 -1.17)	0.099 NS, a	0.88 (0.33 -2.34)	0.804 NS, a	0.51 (0.20 -1.32)	0.161 NS,a
AA (ref)	23 (57.5)	15 (37.5)	14 (35.0)		Ref. (1.00)	-	Ref. (1.00)	-	Ref. (1.00)	-
Dominant*				0.084 NS, a						
GG + AG (var)	17 (42.5)	25 (62.5)	26 (65.0)		0.40 (0.16 -0.98)	**0.044 S, a**	0.90 (0.36 -2.23)	0.816 NS, a	0.44 (0.18 -1.09)	0.073 NS, a
AA (ref)	23 (57.5)	15 (37.5)	14 (35.0)		Ref. (1.00)	-	Ref. (1.00)	-	Ref. (1.00)	-
Recessive**				0.334 NS, a						
GG	3 (7.5)	7 (17.5)	7 (17.5)		0.38 (0.09 -1.60)	0.176 NS, a	1.00 (0.32 -3.17)	1.000 NS, a	0.38 (0.09 -1.60)	0.176 NSa
AA + AG (ref)	37 (92.5)	33 (82.5)	33 (82.5)		Ref. (1.00)	-	Ref. (1.00)	-	Ref. (1.00)	-
Alleles				0.057 NS, a						
G	20 (25.0)	32 (40.0)	33 (41.3)		0.47 (0.24 -0.93)	**0.029 S, a**	0.95 (0.51 -1.78)	0.872 NS, a	0.50 (0.25 -0.98)	**0.043 S,a**
A (ref)	60 (75.0)	48 (60.0)	47 (58.8)		Ref. (1.00)	-	Ref. (1.00)	-	Ref. (1.00)	-
P_{HWE} ***	0.614	0.760	0.971							

a: Pearson Chi-Square test
b: Fisher's Exact test
* : Dominant model: variant type + hetero type vs wild type.
**: Recessive model: variant type vs hetero type + wild type
***: $P_{HWE,}$ for testing Hardy-Weinberg equilibrium
NS: Non significant at P-value ≥ 0.05
S: Significant at P-value < 0.05
HS : Highly significant at P-value < 0.01
var: variant
ref: reference

Association of ACKR1 (DARC) polymorphism (rs12075) with different clinical and laboratory parameters

In the cirrhotic patients group, liver stiffness measurement (LSM) values in addition to FIB4 and APRI scores were significantly lower in patients having GG/AG genotypes with mean values of 16.5 kPa, 2.82, and 1, respectively, compared to AA genotype patients exhibiting mean values of 23.3 kPa, 4.56, and 1.58 (p = 0.004, 0.001, and 0.007, respectively). Moreover, the GG/AG genotype group exhibited reduced levels of total and direct bilirubin and INR, alongside increased white blood cell counts and platelet levels. Consistent with the mentioned results, patients with GG/AG genotypes had a significantly lower mean Child-Pugh-Turcotte score of 7.94 ± 1.52, with 82.4% categorized as class A or B. Conversely, those with the AA genotype had a higher mean score of 10.43 ± 1.50, with 78.3% falling into class C (p < 0.001). In the non-cirrhotic group, similar patterns were noted. GG/AG carriers had significantly lower liver stiffness, FIB-4, and APRI scores (p < 0.001, 0.003, and 0.005, respectively). Liver enzymes (ALT and AST) were also reduced, while serum albumin and platelet counts were elevated in the GG/AG group versus the AA group **(Table 3).**

Table 3: Association of demographic, laboratory, and clinical parameters in cirrhotic and non-cirrhotic patients with DARC rs12075 genotypes

	Cirrhotic patients (F4)			Non- cirrhotic patients (F0 – F3)		
	DARC rs12075 genotypes			DARC rs12075 genotypes		
Characteristics *	**GG/AG (n=17)**	**AA (n=23)**	**P-value**	**GG/AG (n=25)**	**AA (n=15)**	**P-value**
Age (years)	54.94 ± 8.70	57.30 ± 6.58	0.334 NS, a	52.88 ± 7.32	57.00 ± 6.21	0.077 NS, a
Gender (male), [n (%)]	7 (41.2)	15 (65.2)	0.131 NS, b	14 (56.0)	7 (46.7)	0.567 NS, b
LSM (kPa)	16.50 (7.50)	23.30 (11.70)	**0.004** HS, c	5.84 ± 2.23	8.80 ± 2.24	**<0.001** HS, a
Fibrosis stages, [n (%)]			-			**0.015** S, d
F0-F1 (<7.1 kPa)	-	-		16 (64.0)	4 (26.7)	
F2 (7.1–9.4 kPa)	-	-		7 (28.0)	4 (26.7)	
F3 (9.5–12.4 kPa)	-	-		2 (8.0)	7 (46.7)	
F4 (≥ 12.5 kPa)	17 (100.0)	23 (100.0)	-	-	-	
FIB-4 score	2.82 (1.54)	4.56 (2.44)	**0.001** HS, c	1.45 (0.67)	2.37 (1.63)	**0.003** HS, c
APRI score	1.00 (0.76)	1.58 (1.21)	**0.007** HS, c	0.46 (0.19)	0.83 (0.70)	**0.005** HS, c
ALT (U/L)	57.00 (36.50)	63.00 (36.00)	0.366 NS, c	52.00 (15.50)	65.00 (22.00)	**0.011** S, c
AST (U/L)	50.00 (29.00)	51.00 (39.00)	0.494 NS, c	43.00 (11.00)	56.00 (26.00)	**0.031** S, c
GGT (U/L)	65.00 (36.50)	92.00 (38.00)	0.139 NS, c	23.12 ± 5.31	25.67 ± 4.27	0.124 NS, a
Total bilirubin (mg/dL)	1.91 (1.98)	3.56 (3.15)	**0.009** HS, c	0.71 (0.27)	0.77 (0.21)	0.235 NS, c
Direct bilirubin (mg/dL)	1.31 (1.10)	2.20 (2.58)	**0.014** S, c	0.24 (0.07)	0.27 (0.06)	0.096 NS, c
Albumin (g/dL)	3.00 (0.50)	2.50 (0.43)	**0.005** HS, c	3.99 ± 0.36	3.63 ± 0.35	**0.004** HS, a
INR	1.43 (0.58)	1.70 (0.45)	**0.036** S, c	1.05 ± 0.08	1.10 ± 0.14	0.200 NS, a
Blood glucose (mg/dL)	103.00 (41.00)	102.00 (27.00)	0.435 NS, c	96.00 (18.00)	98.00 (29.00)	0.900 NS, c
Hemoglobin (g/dL)	10.99 ± 1.71	10.83 ± 1.38	0.748 NS, a	12.51 ± 1.27	12.75 ± 1.38	0.581 NS, a
WBCs (10^3 cell/µL)	3.90 (0.35)	3.50 (0.90)	**0.046** S, c	7.12 ± 1.85	6.78 ± 1.87	0.578 NS, a
Platelets (10^3 cell/µL)	138.88 ± 46.63	92.13 ± 25.69	**0.001** HS, a	220.88 ± 48.24	170.60 ± 48.52	**0.003** HS, a
HBV/ HCV, [n (%)]	8 (47.1)/ 9 (52.9)	14 (60.9)/ 9 (39.1)	0.385 NS, b	10 (40.0)/ 15 (60.0)	10 (66.7)/ 5 (33.3)	0.102 NS, b
Child score	7.94 ± 1.52	10.43 ± 1.50	**<0.001** HS, a	-	-	
Child classification, [n (%)]			**<0.001** HS, b			-
A/ B	14 (82.4)	5 (21.7)		-	-	
C	3 (17.6)	18 (78.3)		-	-	
Ascites (yes), [n (%)]	8 (47.1)	22 (95.7)	**0.001** HS, d	-	-	-

*Values are expressed as median (interquartile range) unless otherwise indicated
a: Student t-test
b: Pearson's chi square test
c: Mann-Whitney test
d: Fisher's Exact test
NS: Non significant at P-value ≥ 0.05
S: Significant at P-value < 0.05
HS : Highly significant at P-value < 0.01

DISCUSSION

Cirrhosis, a condition defined by progressive liver fibrosis and structural remodeling, represents a critical endpoint in chronic hepatitis. It contributes substantially to global health burdens, being a major driver of complications and death in chronic liver disease[18]. Persistent infections with hepatitis B or C viruses remain the primary culprits behind chronic liver injury, despite the availability of effective antiviral options[19]. Genetic factors can influence how the host responds to viral hepatitis, impacting the course of the infection, fibrosis development, and its progression to liver cirrhosis[20]. Among these genetic factors, single nucleotide polymorphisms (SNPs) in genes that regulate immune or inflammatory pathways have drawn particular interest. One such variant is rs12075 in the DARC gene, which has been linked to fibrosis risk in a Spanish cohort with hepatitis C[13].

In our study, we examined whether this variant influences liver disease severity in an Egyptian cohort with chronic hepatitis due to HBV or HCV infection. We observed that the GG genotype was less prevalent in the cirrhotic group relative to other groups. We further investigated this genetic association in different genetic models (dominant and recessive). When analyzed using a dominant inheritance model (GG + AG vs. AA), the presence of the G allele correlated with a reduced risk of cirrhosis (p = 0.044), consistent with previous findings suggesting a protective role for this allele. Also, the G allele showed a significantly lower frequency among cirrhotic patients compared to controls (p=0.029) as well as non-cirrhotic patients (p=0.043). These results mirror observations by Jiménez-Sousa et al., who

reported a similar protective association of the G allele in a cohort of HCV-infected individuals[13].

In contrast, an earlier investigation failed to find a link between rs12075 and disease severity in HCV, despite its known effect on serum chemokine levels like CCL2. This discrepancy may stem from differences in sample size, population genetics, or study design.[21].

We also assessed the clinical implications of rs12075 variants. Carriers of the GG or AG genotypes consistently showed more favorable liver profiles across both cirrhotic and non-cirrhotic groups. These patients had significantly lower liver stiffness (LSM), lower fibrosis indices (FIB-4, APRI), and higher serum albumin and platelet values than the AA genotype in both patient groups. Also, the GG/AG genotype was linked to markedly reduced liver enzymes (ALT & AST) compared to the AA genotype in non-cirrhotic subjects. Moreover, in the cirrhotic group, it was associated with significantly better child classes than the AA genotype. This indicates the beneficial role of this genotype. Interestingly, while Jiménez-Sousa et al. identified protective genotype effects, their study lacked sufficient clinical detail to assess associations with laboratory or fibrosis-related markers, due to its retrospective design[13]. Our findings therefore extend this line of inquiry by connecting DARC genotype to measurable clinical outcomes in real-time.

A major strength of our study lies in its integrative approach, combining genetic analysis with non-invasive fibrosis scores to assess their collective utility in cirrhosis detection. The use of well-matched control groups and standardized diagnostic criteria adds to the robustness of the findings. Furthermore, our identification of a significant association between the G allele and a reduced probability of cirrhosis establishment provides novel insight into the genetic basis of fibrosis advancement.

However, the study is not without limitations. The statistical power to identify modest genetic connections may be diminished by the tiny sample size, which may also restrict the generalizability of our results. Furthermore, the cross-sectional design limits our capacity to determine causality. Potential confounders, such as coexisting metabolic conditions or other genetic variants, were not fully explored. Future studies with larger, more diverse cohorts and longitudinal follow-up are warranted to confirm and expand on our results.

CONCLUSION

DARC rs12075 SNP could be related to liver fibrosis progression to cirrhosis in chronic viral hepatitis patients. The G allele was substantially less prevalent in patients with cirrhosis, which may have a protective effect against cirrhosis development. Although the genetic association requires further validation in larger populations, our data highlight the potential utility of incorporating genetic profiling alongside clinical assessments to enhance early identification and risk stratification in chronic liver disease.

Declarations:

Consent for publication: Not applicable

Availability of data and material: Data are available upon request.

Competing interests: The author(s) declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

This manuscript has not been previously published and is not under consideration in another journal.

Funding: Authors did not receive any grants from funding agencies.

REFERENCES

1. Ginès P, Krag A, Abraldes JG, Solà E, Fabrellas N, Kamath PS. Liver cirrhosis. Lancet. 2021; 398(10308):1359-1376.
2. Tapper EB, Ufere NN, Huang DQ, Loomba R. Review article: current and emerging therapies for the management of cirrhosis and its complications. Aliment Pharmacol Ther. 2022; 55(9):1099-1115.
3. Akkız H, Gieseler RK, Canbay A. Liver Fibrosis: From Basic Science towards Clinical Progress, Focusing on the Central Role of Hepatic Stellate Cells. Int J Mol Sci.; 25(14):7873.
4. Lee MH, Chen YT, Huang YH, Lu SN, Yang TH, Huang JF, Yin SC, Yeh ML, Huang CF, Dai CY, Chuang WL, Yu ML, Yang HI, Chen HY, Chen CJ. Chronic Viral Hepatitis B and C Outweigh MASLD in the Associated Risk of Cirrhosis and HCC. Clin Gastroenterol Hepatol. 2024; 22(6):1275-1285.e2.
5. Hammerich L, Tacke F. Hepatic inflammatory responses in liver fibrosis. Nat Rev Gastroenterol Hepatol. 2023; 20(10):633-646.
6. Li H, Wu M, Zhao X. Role of chemokine systems in cancer and inflammatory diseases. MedComm (2020). 2022; 3(2):e147.
7. Crawford KS, Volkman BF. Prospects for targeting ACKR1 in cancer and other diseases. Front Immunol. 2023; 14:1111960.
8. Crijns H, Vanheule V, Proost P. Targeting Chemokine-Glycosaminoglycan Interactions to Inhibit Inflammation. Front Immunol. 2020; 11:483.
9. Ntumngia FB, Thomson-Luque R, Pires CV, Adams JH. The role of the human Duffy antigen receptor for chemokines in malaria susceptibility: current opinions and future treatment prospects. J Receptor Ligand Channel Res. 2016; 9:1-11.

10. Bonecchi R, Graham GJ. Atypical Chemokine Receptors and Their Roles in the Resolution of the Inflammatory Response. Front Immunol. 2016; 7:224.
11. Schnabel RB, Baumert J, Barbalic M, Dupuis J, Ellinor PT, Durda P, Dehghan A, Bis JC, Illig T, Morrison AC, Jenny NS, Keaney JF Jr, Gieger C, Tilley C, Yamamoto JF, Khuseyinova N, Heiss G, Doyle M, Blankenberg S, Herder C, Walston JD, Zhu Y, Vasan RS, Klopp N, Boerwinkle E, Larson MG, Psaty BM, Peters A, Ballantyne CM, Witteman JC, Hoogeveen RC, Benjamin EJ, Koenig W, Tracy RP. Duffy antigen receptor for chemokines (Darc) polymorphism regulates circulating concentrations of monocyte chemoattractant protein-1 and other inflammatory mediators. Blood. 2010; 115(26):5289-5299.
12. Poulsen KL, Cajigas-Du Ross CK, Chaney JK, Nagy LE. Role of the chemokine system in liver fibrosis: a narrative review. Dig Med Res. 2022; 5:30.
13. Jiménez-Sousa MÁ, Gómez-Moreno AZ, Pineda-Tenor D, Sánchez-Ruano JJ, Artaza-Varasa T, Martin-Vicente M, Fernández-Rodríguez A, Martínez I, Resino S. Impact of DARC rs12075 Variants on Liver Fibrosis Progression in Patients with Chronic Hepatitis C: A Retrospective Study. Biomolecules. 2019; 9(4):143.
14. Najafi N, Razavi A, Jafarpour H, Raei M, Azizi Z, Davoodi L, Abdollahi A, Frouzanian M. Evaluation of hepatic injury in chronic hepatitis B and C using APRI and FIB-4 indices compared to fibroscan results. Ann Med Surg (Lond). 2024; 86(7):3841-3846.
15. Kim MN. [Noninvasive Imaging Test to Assess Liver Fibrosis: Vibration-controlled Transient Elastography]. Korean J Gastroenterol. 2024; 84(5):201-205.
16. Rinaldi L, Giorgione C, Mormone A, Esposito F, Rinaldi M, Berretta M, Marfella R, Romano C. Non-Invasive Measurement of Hepatic Fibrosis by Transient Elastography: A Narrative Review. Viruses. 2023; 15(8):1730.
17. Tsoris A, Marlar CA. Use Of The Child Pugh Score In Liver Disease. 2023. In: StatPearls [Internet]. PMID: 31194448.
18. Fadlallah H, El Masri D, Bahmad HF, Abou-Kheir W, El Masri J. Update on the Complications and Management of Liver Cirrhosis. Med Sci (Basel). 2025; 13(1):13.
19. Frericks N, Klöhn M, Lange F, Pottkämper L, Carpentier A, Steinmann E. Host-targeting antivirals for chronic viral infections of the liver. Antiviral Res. 2025; 234:106062.
20. Gan C, Yuan Y, Shen H, Gao J, Kong X, Che Z, Guo Y, Wang H, Dong E, Xiao J. Liver diseases: epidemiology, causes, trends and predictions. Signal Transduct Target Ther. 2025; 10(1):33.
21. Lettow I, Berres ML, Schmitz P, Müller T, Berg T, Neumann UP, Trautwein C, Wasmuth HE. A Duffy antigen receptor for chemokines (DARC) polymorphism that determines pro-fibrotic chemokine serum concentrations is not directly associated with severity of hepatitis C infection. Hum Immunol. 2011; 72(3):273-7.