

Association of the degree of liver fibrosis evaluated by elastography with carotid intima media thickening in hepatitis C patients

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Abstract

Objective: To evaluate the degree of liver fibrosis and carotid intima-media thickness in patients with hepatitis C virus, and to assess the correlation between the degree of fibrosis and carotid intima-media thickness.

Method: The cross-sectional study was conducted at the Dow University of Health Sciences, Karachi, from August 2018 to August 2020, and comprised healthy volunteers as controls in group A, and diagnosed chronic hepatitis C virus patients in group B. Those in group B were further divided based on Metavir fibrosis staging into group B1 comprising those with stages 1 and 2, and group B2 comprising those with stages 3 and 4. Liver fibrosis was quantitatively measured as liver stiffness via elastography, and carotid atherosclerosis was evaluated using B-mode carotid ultrasonography. The relationship between liver fibrosis and carotid intima-media thickness was assessed. Data was analysed using SPSS 22.

Results: Of the 90 subjects, 30(33.3%) were in group A; 16(53.3%) females and 14(46.7%) males with overall mean age of 45.8±8.2 years. There were 29(32.2%) patients in group B1; 15(51.7%) females and 14(48.3%) males with overall mean age of 45.7±11.0 years. There were 31(34.4%) patients in group B2; 19(61.3%) males and 12(48.3%) females with overall mean age of 50.4±7.0 years ($p>0.05$). Liver stiffness was significantly higher in group B2 compared to groups A and B1 ($p=0.000$). Carotid intima-media thickness was significantly increased in group B compared to group A ($p=0.001$), but no significant difference was noted between groups B1 and B2 ($p=0.227$). Carotid intima-media thickness showed a weak, non-significant positive correlation with fibrosis severity ($r=0.021$; $p=0.178$).

Conclusion: Hepatitis C virus infection was found to be significantly associated with increased carotid intima-media thickness, but no significant correlation was observed between liver fibrosis severity and carotid intima-media thickness.

Keywords: HCV, Elastography, Carotid intima and media thickening. (JPMA 76: 1669; 2026)

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Introduction

Transformation of liver parenchymal cells by fibrous tissues is a dynamic and progressive process in patients with chronic liver diseases (CLD). It represents a critical milestone not only in predicting the disease prognosis, but also in defining the clinical management and in guiding appropriate treatment decisions.¹ Therefore, precise evaluation of liver fibrosis severity is crucial in clinical practice.

Traditionally, the extent of fibrosis is determined by liver biopsy, which is widely considered the gold standard for the histological assessment of hepatic fibrosis severity. However, it has several limitations, including its invasive nature, risk of complications, and sampling variability, which limit its acceptability in routine clinical practice. In the light of these drawbacks, various non-invasive modalities have recently been recommended as reliable

alternative approaches for the diagnosis and staging of hepatic fibrosis, offering safer and more reproducible means of evaluation.²

Elastography is a non-invasive, painless and highly reproducible approach which measures the firmness of liver parenchyma. Elastography-measured liver stiffness was found to be correlated with the degree of fibrosis in numerous studies, allowing for the staging of liver disease by Metavir fibrosis scoring scale.³ Via this procedure, almost 100 times more volume of liver parenchyma can be examined compared to a biopsy.⁴

Hepatocytes are not the only target of HCV as the virus is found to be involved in various extrahepatic manifestations as well. Thus, in contrast to earlier published studies that documented the protection of hepatitis C virus (HCV) patients from cardiovascular events,⁵ recent data reported increased risk among HCV patients of coronary artery diseases (CADs).⁶ It is, therefore, recommended that HCV patients should be evaluated for cardiovascular disease (CVD) risk even in the absence of the symptoms.

The risk of CVDs is evaluated by a number of invasive and non-invasive imaging techniques, including the measurement of carotid arteries. Carotid intima-media

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thickness (CIMT) is one of the simplest and inexpensive markers for the non-invasive evaluation of CVD risk. The measurement of CIMT has been recommended by the American Heart Association (AHA) for the evaluation of initial or subclinical atherosclerosis.⁷

Different studies stated that HCV patients had higher mean CIMT values not affected by age, gender and metabolic risk factors, and corroborated the association of HCV infection with atherosclerosis.^{8,9}

Despite a large number of studies,⁷⁻⁹ the relation between the degree of liver fibrosis, determined by elastography, and the severity of atherosclerosis, determined by CIMT, to our knowledge, has not been extensively explored. The current study was planned to fill the gap in literature by determining the degree of stiffness or fibrosis of hepatic parenchyma among HCV-infected patients, to assess the degree of atherosclerosis using CIMT scans, and to explore the correlation between the degree of hepatic fibrosis and CIMT assessment.

Patients and Methods

The descriptive, observational, cross-sectional study was conducted at the Institute of Basic Medical Sciences, Dow University of Health Sciences (DUHS), Karachi, from August 2018 to 2020. After approval from the institutional ethics review board, the sample size was determined using the PASS version II calculator,¹⁰ based on expected effect sizes from a previous study¹¹ reporting mean CIMT (in cirrhotic 11.9 ± 1.8 , non-cirrhotic 8.2 ± 1.4 , control 6.2 ± 2.7) with 99% power and 0.01 significance level using F-test, assuming a common standard deviation (SD) of ± 2.36 . The sample size was inflated to improve statistical power, reduce type II error, and allow subgroup analysis based on fibrosis staging. Post-hoc power analysis using the final sample size showed a study power of >90%. The sample was raised using non-probability convenience sampling technique from among those of either gender aged 30-60 years visiting the hepatitis clinic or the medical ward of Ruth Pfau Civil Hospital, Karachi. The sample comprised healthy volunteers as controls in group A, and diagnosed chronic hepatitis C (CHC) patients in group B. The groups were matched for age and gender during the recruitment phase to minimise confounding. Those in group B were subjected to elastography, and liver stiffness was graded using the Metavir score: F1 = 5.3-7.1kPa, F2 = 7.0-8.5kPa, F3 = 9.5-11.6kPa, and F4 = 13.1-18.8kPa.¹² Those with F1 and F2 staged were placed in group B1, while those with F3 and F4 stages comprised group B2.

Patients with a history of hypertension, smoking, ascites, alcohol use, co-infection with other types of hepatitis viruses, pregnant women and those unwilling to

participate were excluded. Following the acquisition of informed consent, the weight and height of the patients were recorded to calculate their body mass index (BMI).

Hepatic elastography and CIMT measurement, according to the recommendations of the World Federation for Ultrasound in Medicine and Biology (WFUMB)¹³ were performed using Supersonic Imaging Aixplorer® ultrasound system (SuperSonic Imagine, Aix-en-Provence, France; currently part of Hologic Inc., USA) after real-time ultrasound of liver.

Liver elastography was performed using an curvilinear transducer (SC6-1, 1-6MHz). After applying gel, the probe was placed on the right hypochondrium, and the patients were instructed to hold their breath to minimise motion artifacts. Elasticity measurements were obtained from three hepatic segments (V, VI, VII, or VIII) 1-3cm beneath the liver capsule. A rectangular ROI (region of interest) was placed on shear wave elastography (SWE) images, followed by a circular ROI (12-14mm) for measurement. Vessels, bile ducts and artifacts were carefully avoided. Three measurements were taken per segment, and SWE was considered successful if >90% of the ROI was filled with colour. Mean kPa values were recorded, and the median value of three valid measurements was used for analysis as the Metavir score.

CIMT was measured by a high-resolution B-mode system equipped with a linear array transducer with frequency >7MHz. During the CIMT measurement, the patients were placed in a supine position with their heads hyperextended and rotated 45 degrees away from the side under examination. Following gel application, the probe was positioned at the midline of the neck, and a lateral probe position was used to obtain optimal image resolution for CIMT measurements. To ensure accurate and consistent CIMT measurements, the bifurcation of the carotid artery was used as a landmark in the image plane. The machine's auto-setting was used to measure a straight, far wall arterial segment that was 10mm in length. Three readings of CIMT were taken for both common carotid arteries (right and left), at end-diastole from plaque-free arterial segments, and these values were averaged to obtain the mean CIMT values that were used for analysis.

Data was analysed using SPSS 22. Comparisons among the groups were done using one-way analysis of variance (ANOVA). Pearson's correlation was used to assess the relationship between liver fibrosis and CIMT. $P < 0.05$ was considered statistically significant.

Result

Of the 90 subjects, 30(33.3%) were in group A; 16(53.3%)

Table-1: Demographic and anthropometric characteristics of the study groups (n=90).

Variables	Group A Control (n=30)	Group B 1 Early Fibrosis F1+F2 (n=29)	Group B 2 Late Fibrosis F3+F4 (n=31)	f-value	p-value
Age (years)	45.8±8.2	45.7±11.0	50.4±7.0	2.74	0.070
Male	14 (46.7%)	14 (48.3%)	19 (61.3%)	1.57	0.455
Female	16 (53.3%)	15 (51.7%)	12 (48.3%)		
BMI	25.5 ± 4.4	26.0±3.2	26.1±3.9	0.33	0.715

BMI: Body mass index.

Table-2: Comparison of mean liver elasticity across the groups.

Variable	Group A Control (n=30)	Group B 1 Early Fibrosis F1+F2 (n=29)	Group B 2 Late Fibrosis F3+F4 (n=31)	f-value	p-value
Mean	5.45±3.8	6.37±1.1	22.6±9.1	163.3	0.000
Degree of Fibrosis					

Table-3: Post-hoc multiple comparison of mean liver elasticity among the groups.

Variables	liver fibrosis		p-value
Liver elasticity (kPa)	Group A (control)	Group B1(early fibrosis)	0.789
	Group A (control)	Group B2(late fibrosis)	0.000
	Group B1 (early fibrosis)	Group B2(late fibrosis)	0.000

Table-4: Post-hoc multiple comparison of mean CINT.

Variables	liver fibrosis		p-value
CINT (mm)	Group A (control)	Group B1 (early fibrosis)	0.000
	Group A (control)	Group B2 (late fibrosis)	0.000
	Group B1(early fibrosis)	Group B2 (late fibrosis)	0.227

CINT: Carotid intima-media thickness.

Table-5: Correlation of CINT in HCV patients with the degree of fibrosis.

Parameter	r-value	R2-value	% of determination	p-value	Significance
CINT	0.143	0.021	2.1%	0.178	Non-significant

CINT: Carotid intima-media thickness, HCV: Hepatitis C virus.

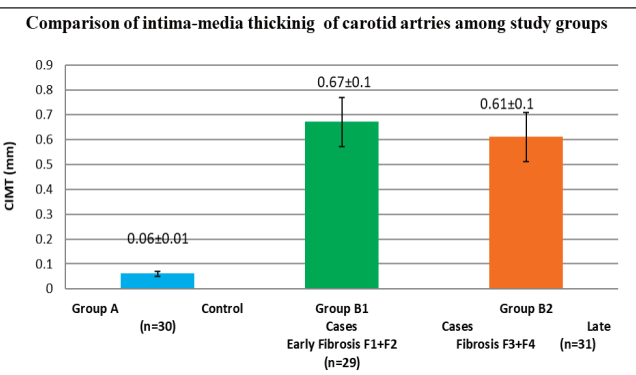


Figure: Intergroup comparison of carotid intima-media thickness (CINT).

Ferraioli G, Barr RG, Berzigotti A, Sporea I, Wong VW, Reiberger T, Karlas T, Thiele M, Cardoso AC, Ayonrinde OT, Castera L. WFUMB guideline/guidance on liver multiparametric ultrasound: Part 1. Update to 2018 guidelines on liver ultrasound elastography. *Ultrasound in medicine & biology*. 2024 Aug 1;50(8):1071-87.

females and 14(46.7%) males with overall mean age 45.8±8.2 years. There were 29(32.2%) patients in group B1; 15(51.7%) females and 14(48.3%) males with overall mean age 45.7±11.0 years. There were 31(34.4%) patients in group B2; 19(61.3%) males and 12(48.3%) females with overall mean age 50.4±7.0 years ($p>0.05$) (Table 1).

Liver stiffness was significantly higher in group B2 compared to groups A and B1 ($p=0.001$) (Table 2). Patients in group B1 had non-significantly raised liver stiffness compared to group A ($p=0.789$) (Table 3).

A significant difference in CINT was noted among the groups (Figure) except between groups B1 and B2 ($p=0.227$) (Table 4).

CINT showed a weak, non-significant positive correlation with fibrosis severity ($r=0.021$; $p=0.178$) (Table 5).

Discussion

In the present study, the participants were categorised on the basis of Metavir classification into early and late fibrosis group. CHC patients had significantly raised mean elastography value compared to the healthy controls. Significance in mean difference in elastography values persisted when the patients were categorised into early and late fibrosis subgroups compared to the controls.

With growing body of data, vascular involvement as extrahepatic manifestation of HCV has revealed that 1.5 million disability-adjusted life years (DALYs) are lost per year due to HCV-associated CVD.¹⁴ The current findings could significantly influence patient management strategies, potentially reducing future morbidity and mortality.

Literature from various regions of the world has reported contrasting findings related to the relation of CHC with atherosclerosis.¹⁵ These contradictions among reports may be attributed to the selection of patients, their duration of illness, presence of human immunodeficiency virus (HIV) co-infection, duration and type of treatment, evaluation of the severity of liver disease by different modalities (invasive/non-invasive) and the presence of different genotypes in different studies. Thus, such findings may not be generalised to the local population.

Patients infected with the HCV are generally recognised to be at the risk of developing liver-related complications, such as cirrhosis and hepatocellular carcinoma (HCC). However, a growing body of evidence has also highlighted numerous extrahepatic manifestations associated with HCV infection.¹⁴ Some of these conditions are well-documented and relatively common, while others are infrequent, or their association with HCV remains unproven. In HCV patients, however, numerous studies

have observed the relation between HCV infection and carotid atherosclerosis with contrasting results.¹⁶ Consistent with the current findings, Poznyak Av et al. reported higher prevalence of carotid plaque among subjects who were positive for HCV-antibody or HCV core antigen than among control subjects.¹⁷ According to the World Health Organisation (WHO), only 16% patients with CHC infection developed cirrhosis with only a proportion of these individuals dying from the liver disease.¹⁸ Vascular disease is the leading cause of death in patients with CHC.¹⁹

Consistent with the current findings, Rajewski P et al. found HCV to be a risk factor for atherosclerosis.²⁰ While, a population-based study demonstrated that patients with CHC infection had significantly decreased CIMT compared to the non-infected subjects.²¹

Atherosclerosis in CHC patients is promoted by several mechanisms, like promotion of HCV endocytosis by low density lipoprotein (LDL) receptor and induction of oxidative stress by HCV core protein along with systemic vasculitides, increased concentration of soluble intracellular adhesion molecules and presence of anti-endothelial antibodies.²² The current finding about CIMT in CHC patients is also in agreement with the findings of Medhioub M et al. who in 2021 reported significantly raised CIMT in CHC patients.⁸ In agreement with the current findings, Wen et al. conducted a meta-analysis demonstrating that HCV infection increases the risk of CAD by 25% in cohort studies, and by 94% in case-control and cross-sectional studies.²³ Similarly, Lee et al. reported that HCV infection is associated with a 28% higher risk of atherosclerotic CVD, contributing to 1.5 million DALYs globally.²⁴ Wang CW et al. found that HCV infection, particularly when combined with metabolic syndrome or liver fibrosis, is significantly associated with coronary and thoracic aortic atherosclerosis.²⁵ These studies collectively underscore the role of HCV as a non-traditional risk factor for atherosclerosis and cardiovascular mortality.

In the present study, the absence of a significant correlation between CIMT and the severity of liver fibrosis among CHC patients aligns with earlier findings by Xin Z et al.²⁶ Conversely, the current findings contrast with those of Petta et al. who reported that severe hepatic fibrosis was associated with a higher risk of carotid atherosclerosis in CHC patients²⁷ and indicated a significant relationship between advanced fibrosis stages and increased CIMT, highlighting the potential role of liver fibrosis in the development of subclinical atherosclerosis.

Several factors may account for the lack of significant correlation observed in the current study. First, the study included HCV patients categorised into early and late

fibrosis groups based on elastography values. However, the number of participants with severe fibrosis was relatively small, potentially limiting the statistical power to detect a significant association. Future studies with larger sample sizes and a higher proportion of patients with advanced fibrosis are warranted to conclusively determine the relationship between liver fibrosis severity and CIMT.

Second, literature suggests that the intensity of HCV infection, as indicated by serum HCV ribonucleic acid (RNA) levels, may be more closely associated with the progression of atherosclerosis than the mere presence of the virus. A 30-month follow-up study demonstrated that individuals exposed to a higher number of infectious pathogens, including HCV, had an increased risk of developing atherosclerosis.²⁸ This dose-response relationship underscores the importance of viral load in the pathogenesis of atherosclerotic changes.

Third, the distribution of different HCV genotypes in the current sample may also have influenced the observed lack of significant association. Genotype 3 was the most prevalent in the cohort. While this genotype has been conclusively linked to HCC, its relationship with atherosclerotic vascular disease and other extrahepatic manifestations remains less clear.²⁹ Further research is needed to elucidate the potential impact of HCV genotype 3 on cardiovascular outcomes.

Also, in terms of limitations, inter- and intra-observer variability assessments in the current study were not formally calculated. And, due to a small sample size and exploratory nature of the study, multivariate analysis was not performed. Finally, genotype-specific analysis was not carried out due to the small sample size.

Conclusion

HCV was found to cause hepatic complications, such as hepatic fibrosis or cirrhosis, and was also significantly associated with increased CIMT. The severity of fibrosis, as determined by Metavir score, was not associated with subclinical atherosclerosis determined by CIMT. Clinicians should evaluate atherosclerosis in CHC patients regardless of the severity of fibrosis.

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Author Contribution:

TS: Concept, design, data acquisition, analysis, interpretation, drafting and final approval.

AA: Drafting and final approval.

SF, HA, FM & NN: Revision and rechecking.