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Relation of Hepatitis C and its Severity Assessed by PCR to the Presence and Severity of Coronary Artery Disease Assessed by Syntax Score

Ahmed Mohamed Onsy, Adham Ahmed Abdeltawab, Abd El-Salam Gebril Senussi
Department of Cardiovascular Diseases, Faculty of Medicine - Ain Shams University

ABSTRACT

Background: Egypt has the highest prevalence rate of hepatitis C virus in the world, making it the most challenging public health problem facing the country. Cardiovascular disease continues to be the principal cause of death worldwide. Several studies have been conducted to confirm, or disprove, an independent association between HCV infection and atherosclerotic disorders, including coronary artery disease.

Objective: the aim of this study was to assess the correlation between hepatitis C virus infection severity and extent of coronary artery disease.

Patients and Methods: this prospective study was carried out in the Cardiovascular Diseases Unit in Ain Shams University Hospitals. This study involved sixty one patients with positive test for HCV antibodies.

Results: PCR level was highly correlated to the absolute Syntax score (SS) and to the Syntax score group, yet it was not found to be significantly correlated to the presence of significant coronary lesion nor to the number of vessels affected. On the other hand SS was highly correlated to the presence of significant coronary lesion and to the number of vessels affected.

Keywords: coronary artery disease, extrahepatic manifestation, hepatitis C virus , oxidized LDL - SYNTAX SCORE.

INTRODUCTION

Hepatitis C has been declared as a global health problem by the World Health Organization, with about 3% of the world's population.The situation is quite worse in Egypt, the national prevalence rate of HCV antibody positively has been estimated to be 10-13 % [(1)]. After infection, the majority of HCV-infected patients develop chronic infection, manifested by the persistence of HCV RNA in the blood [(2)].

The association between hepatitis C virus (HCV) infection and coronary artery disease (CAD) is controversial. Very recent data have indicated that HCV infection was associated with a higher risk of CHD, after the adjustment of traditional risk factors , and seropositivity for HCV may have a role in the pathogenesis of carotid atherosclerosis [(3)].

Furthermore; HCV infection may independently predict an increased severity of CHD [(3)]. Approximately 150 million people worldwide have chronic hepatitis C infection, roughly 1 person in 50 is infected with the hepatitis C virus [(4)].

Egypt has the highest prevalence rate of hepatitis C virus in the world, making it the most challenging pupil health problem facing the country [(5)].

A study showed that 14.7% of the Egyptian population carry HCV antibodies and 9.8% have an active infection. There is an evidence for variation in the course of infection associated with different HCV variants (genotypes)

and in response to treatment with interferon[(6)]. In the Middle East almost all anti-HCV positive individuals are infected with type 4 [(7)]. Individuals with HCV face common comorbidities such as cardiovascular diseases. It is unknown how infection with HCV affects coronary heart disease (CHD) progression and outcomes [(8)]. Infectious etiologies have been hypothesized to contribute to the inflammatory cascade leading to atherosclerosis [(9)].

Hepatitis C virus (HCV) is the cause of many different forms of heart disease worldwide and yet few cardiologists are aware of it as an etiology of heart disease, or its treatment. The burden of HCV-derived heart diseases is global, with a higher prevalence in Asia, Africa, and low- and middle-income countries [(10)]. Egypt has the highest prevalence of HCV in the world, apparently due to previous mass parenteral anti-schistosomal therapy [(11)].

Hepatitis C virus (HCV) RNA is the most important indicator of viral replication in patients with hepatitis C. HCV RNA, which is a significant parameter in terms of detection of viremia in serum, the trend of the infection, can be quantitatively detected with polymerase chain reaction (PCR) [(12)].

Understanding the mutual relationship between the liver and the heart is important for

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both hepatologists and cardiologists. Hepato-cardiac diseases can be classified into heart diseases affecting the liver, liver diseases affecting the heart, and conditions affecting the heart and the liver at the same time [13].

Chronic liver diseases may affect cardiac functions in the absence of other heart disease. These effects are called cirrhotic cardiomyopathy and may aggravate the course during orthotropic liver transplantation (OLT). Most of these effects are reversed after OLT [14].

AIM OF THE WORK

This study aimed to assess the correlation between hepatitis C virus infection severity and extent of coronary artery disease among patients presenting to Ain Shams University cath lab for coronary angiography or PCI.

PATIENTS and METHODS

Research Design: this prospective cohort study was designed to determine how hepatitis C and its severity assessed by PCR influence disease progression and severity in persons with coronary disease being assessed by Syntax Score.

Research setting: this study was carried out in the Cardiovascular Diseases Unit in Ain Shams University Hospitals**,** starting November 2015 until September 2017. The severity of CAD as assessed by Syntax score and the level of HCV RNA as detected by quantitative PCR were compared among sixty one patients with positive HCV antibody test attended in Ain Shams University hospitals for elective coronary angiography.

Ethical statement Informed consent was obtained from each individual participating in the study. The study was approved by the Ethics Board of Ain Shams University.

Patients: The study involved sixty one patients presented to Ain Shams University catheterization lab for elective coronary angiography or PCI. **Inclusion criteria of the study:** stable clinical condition,patient diagnosed to have HCV infection by HCV antibodies and indication for elective coronary angiography. **Exclusion criteria:** patients presented with critical illness or hemodynamic instability, surgery or trauma within the previous month, known cancer, or hepatic failure, severe liver damage and cirrhosis, acute or chronic inflammatory disease, immunological disease, and history or presence of neoplastic disease, patients refusal to do catheterisation and refusal to be added to the study, chronic renal failure on dialysis and age less than18 years, or more than 80 years.

METHODOLOGY

all patients were subjected to proper history taking*:* all subjects gave a complete history which included: age and sex. Special habits included: smoking/tobacco and alcohol consumption and family history of ischemic heart disease, assessment of presenting complaints as chest, other symptoms as dyspnea on exertion, history of medical diseases: included arterial hypertention and history of drug therapy.

Complete clinical examinations were done and included: general examination, blood pressure measurement using mercurial sphygmomanometer, pulse rate and body temperature, peripheral pulse examination, weight, height and BMI, abdominal examination and local cardiac examination.

Labs*:* blood samples were collected using standard technique into tubes containing EDTA for necessary investigations**.** Complete blood count, HCV RNA and serum creatinine levels were obtained from all patients. **Confirmation of positivity for hepatitis C**; HCV serostatus were determined from documentation of a prior positive HCV antibody test in the patient's medical record. **Measurement of PCR:** estimation of serum HCV RNA by quantitative viral load tests (Polymerase chain reaction (PCR). These tests measured the amount of virus in one milliliter of blood, which indicated current active infection. This type of quantitative PCR test is very sensitive and can measure as few as 50 IU/ml. Under detectable level, < 50 IU is considered negative, low viremia< 100,000 IU/ml, moderate viremia from 100,000 to 1,000,000 IU/ml and marked viremia> 1,000,000IU/ml [15]. Quantitative viral load tests (Polymerase chain reaction (PCR) levels were measured with the American; The StepOne™ Real-Time PCR System API7000, applied biosystems, Life Technologies Corporation, USA**.**

Coronary angiography*:* all patients underwent elective coronary angiography in different views and projections using seldinger technique. Significant lesions were defined as a 50% or greater stenosis in the luminal diameter of any major epicardial coronary artery. Presence of significant lesions was determined based on visual estimation. Syntax score was calculated for every patient with significant CAD using dedicated software.

RESULTS

Table 1: number and percentage of males and females and prevalence of hypertention and smoking.

		No. = 61
Age	Mean±SD	59.48 ± 8.13
	Range	38 – 75
Sex	Female	17 (27.9%)
	Male	44 (72.1%)
HTN	Negative	50 (82.0%)
	Positive	11 (18.0%)
Smoking	Non smoker	45 (73.8%)
	Smoker	16 (26.2%)

Table 2: examination data of patients

		No. = 61
HR(B/M)	Mean±SD	71.74 ± 8.28
	Range	60 – 96
Systolic BP (mmhg)	Mean±SD	130.08 ± 12.37
	Range	110 – 150
Diastolic BP (mmhg)	Mean±SD	78.20 ± 8.90
	Range	60 – 100
BW(Kg)	Mean±SD	82.33 ± 9.18
	Range	68 – 125
HT(M)	Mean±SD	1.77 ± 0.05
	Range	1.68 – 1.86
BMI	Mean±SD	26.13 ± 2.34
	Range	22.5 – 36

Table 3: lab. results of the patients

		No. = 61
Hb (gm/dl)	Mean±SD	13.69 ± 1.27
	Range	11.7 – 16
WBC	Mean±SD	6.17 ± 1.25
	Range	4 – 8.8
PCR Result(U/L)	Median(IQR)	20000 (16 – 215400)
	Range	16 – 2540000
PCR interpretation	Un detectable	26 (42.6%)
	Low	11 (18.0%)
	Moderate	19 (31.1%)
	High	5 (8.2%)

Table 4: result of coronary angiography

		No. = 61
Significant lesion	No	18 (29.5%)
	Yes	43 (70.5%)
Number of vessels	No vessels affected	18 (29.5%)
	One vessel affected	10 (16.4%)
	Two vessels affected	15 (24.6%)
	Three vessels affected	18 (29.5%)
Syntax Score	Median(IQR)	16.00 (0 - 25)
	Range	0.00 – 43.00
Syntax groups	Syntax < 23	40 (65.6%)
	Syntax 23 - 32	14 (23.0%)
	Syntax > 32	7 (11.5%)

Table 5: correlation between PCR and demographic data

		PCR interpretation				Test value	P-value	Sig.
		Undetectable	Low	Moderate	High			
		No. = 26	No. = 11	No. = 19	No. = 5			
Age	Mean±SD Range	58.38 ± 8.86 38 – 72	61.18 ± 8.40 45 – 75	59.84 ± 8.09 40 – 70	60.00 ± 3.67 54 – 63	0.326•	0.807	NS
Sex	Female Male	7 (26.9%) 19 (73.1%)	3 (27.3%) 8 (72.7%)	6 (31.6%) 13 (68.4%)	1 (20.0%) 4 (80.0%)	0.298*	0.960	NS
HTN	Negative Positive	22 (84.6%) 4 (15.4%)	10 (90.9%) 1 (9.1%)	13 (68.4%) 6 (31.6%)	5 (100.0%) 0 (0.0%)	4.177*	0.243	NS
Smoking	Non smoker Smoker	20 (76.9%) 6 (23.1%)	10 (90.9%) 1 (9.1%)	14 (73.7%) 5 (26.3%)	1 (20.0%) 4 (80.0%)	9.275*	0.026	S

Table 6: correlation between SS and demographic variables

		Syntax < 23	Syntax 23 - 32	Syntax > 32	Test value	P-value	Sig.
		No. = 40	No. = 14	No. = 7			
Age	Mean ±SD Range	58.95 ± 9.15 38 – 75	59.29 ± 6.37 48 – 70	62.86 ± 3.72 59 – 70	0.685•	0.508	NS
Sex	Female Male	11 (27.5%) 29 (72.5%)	4 (28.6%) 10 (71.4%)	2 (28.6%) 5 (71.4%)	0.008*	0.996	NS
HTN	Negative Positive	35 (87.5%) 5 (12.5%)	12 (85.7%) 2 (14.3%)	3 (42.9%) 4 (57.1%)	8.205*	0.017	S
Smoking	Non smoker	34 (85.0%) 6 (15.0%)	9 (64.3%) 5 (35.7%)	2 (28.6%) 5 (71.4%)	10.648*	0.005	HS

Table 7: correlation between angiographic data and result of PCR

		PCR interpretation				Test value	P-value	Sig.
		Un-detectable	Low	Moderate	High			
		No. = 26	No. = 11	No. = 19	No. = 5			
Significant lesion	No Yes	11 (42.3%) 15 (57.7%)	4 (36.4%) 7 (63.6%)	3 (15.8%) 16 (84.2%)	0 (0.0%) 5 (100.0%)	6.108*	0.106	NS
Number of vessels	No vessels affected One vessel affected Two vessels affected Three vessels affected	11 (42.3%) 6 (23.1%) 5 (19.2%) 4 (15.4%)	4 (36.4%) 3 (27.3%) 2 (18.2%) 2 (18.2%)	3 (15.8%) 0 (0.0%) 7 (36.8%) 9 (47.4%)	0 (0.0%) 1 (20.0%) 1 (20.0%) 3 (60.0%)	16.518*	0.057	NS
Syntax Score	Median(IQR) Range	5 (0 - 16) 0 – 25	6 (0 - 18) 0 – 25	27 (17 - 36) 0 – 39	29 (28 – 33) 25 – 43	24.572‡	0.001	HS
Syntax groups	Syntax < 23 Syntax 23 - 32 Syntax > 32	24 (92.3%) 2 (7.7%) 0 (0.0%)	10 (90.9%) 1 (9.1%) 0 (0.0%)	6 (31.6%) 7 (36.8%) 6 (31.6%)	0 (0.0%) 4 (80.0%) 1 (20.0%)	34.038*	0.001	HS

DISCUSSION

This prospective cohort study was conducted to determine how hepatitis C and its severity assessed by PCR influence disease progression in persons with coronary artery disease being assessed by Syntax Score. This study was carried out in the Cardiovascular Diseases Unit in Ain Shams University Hospitals**,** from November 2015 until September 2017.

The severity of CAD as assessed by Syntax Score and the level of HCV RNA as detected by quantitative PCR were compared among sixty one patients with positive HCV antibody test attended in Ain Shams University Hospitals for elective coronary angiography.

Mean age of patients enrolled in the present study was 59.48 ± 8.13 and it ranged from 38 to75 years. Most patients were males (72.1%).

Several studies have evaluated the association between HCV and CAD. CAD was defined variably among the studies.

Vassalle *et al.* [(2)] investigated the association between HCV infection and coronary artery disease (CAD) in a case control study of 491 patients with angiographic documentation of CAD (stenosis >50%) and the control group of 195 patients admitted to the same institute for reasons other than suspected CAD, the mean age of study population was 66, 81.3% of them were males. The same authors assessed the prevalence of HCV seropositivity in CAD patients VS. controls **.**

Momiyama *et al.* compared the prevalence of HCV antibody positivity among angiographically documented CAD (at least 50% stenosis in a major coronary artery) 524 patients and106 as controls, with mean age of 64 and 84% of them were males [(16)]. Another case control was done by **Arcari *et al.*** who compared the prevalence of HCV infection between292 MI patients VS. control group of 290 subjects, the study included young, active-duty USA military personnel, all subjects were males and 60.6% of the study population were white, 30.1% were black and 9.25% for others, the mean age was 42.2 years [(17)]**.**

Another study was conducted in Turkey between 2003 and 2007 by **Alyan *et al.*** enrolled 364 CAD patients (139 HCV antibody positive patients VS. 225HCV negative patients as control) the mean age of study population was 61.2 years and 76.3% were males. %.All patient underwent coronary angiography and the rate of multi-vessel disease and Reardon severity score were compared in HCV antibody positive patients VS uninfected control group, after adjustment for age, sex, smoking, hypertension, DM, body mass index (BMI), CRP and fibrinogen [(18)]**.**

In a US retrospective cohort of 171665 subjects (HCV infected: 82089 and controls: 89582),with mean age of 51.2 years and 97.2% were males, White constitute 55.4%,29.5 were black and hispanic were 1.9. **Butt *et al.*** assessed the risk of CAD in both groups from 2001 to2006 after adjusting traditional risk factors [(3)]**.**

A community based long term prospective study in a cohort of 23820 Taiwanese adults, enrolled from 1991 to 1992 with follow-up data up to 2008, the study investigated all causes of mortality in anti-HCV positives compared to anti-HCV negatives [(19)]. In a large retrospective cohort study from the United States of America (USA) **Pothineni *et al.*** enrolled 24484 patients who further subdivided into three groups (HCV antibody positive: 8251, HCV RNA positive: 1434, and a controls: 14799), the mean age of the study population was 47.3 year for HCV antibody positive group and 48.6 for HCV-RNA positive group and the percentage of male was56.3% and 57% in both groups respectively, white Americans constitute about 77%, African Americans were18.5%, the incidence of CAD compared among these three groups [(20)]**.**

Another prospective study by Moumen [(1)]conducted in Sohag University Hospitals from May 2012 until May 2015, the study population comprised 100 patients with angiographically documented CAD (>50%stenosis).

These subjects were further subdivided into 50 HCV RNA negative patients and 50 HCV RNA positive patients as detected by Polymerase Chain Reaction (PCR). HCV RNA positive patients were further classified according to level of HCV RNA to low, moderate and high viremia. The severity of CAD, level of hsCRP as well as level of serum GGT were compared among negative HCV RNA and positive HCV RNA as detected by PCR [(21)]**.**

The majority of patients in the present study were non- hypertensive 82%, with prevalence of non-smokers (73.8%).

Among patients included in this study 75% presented by chest pain and 62% of patients had history of breathlessness.The mean body mass index of patients was 26.13 ± 2.34. More than two third of patients had significant lesion(s) on coronary angiography (70.5%). Patients who had three vessels disease were eighteen (29.5%),

those with two vessels disease were fifteen (24.6%) and those who had one vessel disease were ten patients (16.4%).

The present study revealed that PCR results was significantly correlated to smoking, it also showed significantly correlation between Syntax score and the presence of hypertension and smoking. On the other hand SS was highly correlated to the presence of significant coronary lesion and to the number of vessels affected.

The most important finding of the present study was that PCR level (viral load) was highly correlated to the absolute SS and to the SS group, yet it was not found to be significantly correlated to the presence of significant coronary lesion nor to the number of affected vessels .The present study showed significant relation between HCV RNA and CAD being assessed by SS and that patients with detectable HCV RNA had a significantly higher SS compared to those with only HCV antibody positive but no detectable RNA. These findings agree with the results of many studies investigated the possible association between HCV infection and CAD, as that by **Vassalle *et al.*** [(2)], which reported a significant high prevalence of HCV seropositivity in the CAD group compared to the controls (6.3% vs 2.0%).

Similar results were reported by **Alyan *et al.*** [(18)] which demonstrated that HCV infection was an independent predictor of severity of coronary atherosclerosis, and that HCV infected patients had higher serum levels of both C reactive protein and fibrinogen and a higher Reardon severity score compared to the uninfected patients.

In a study done by **Butt *et al.*** [(3)]**,** the authors reported a significant higher risk of incidental CAD in HCV infected subjects compared to those who were uninfected, despite the better metabolic profile reported in the 1st group and furthermore; HCV infection may independently predict an increased severity of CHD.

Interestingly, **Lee *et al.*** [(19)] reported that anti-HCV positives had a higher mortality from both hepatic and extrahepatic diseases compared to anti-HCV negatives, showing an adjusted HR of 1.50 for circulatory diseases.The same authors highlighted that this increase in mortality from circulatory diseases was maintained in anti-HCV patients with detectable HCV RNA, but not in those with undetectable HCVRNA.

Pothineni *et al.* [(20)] reported that not only positive HCV antibody, but also on measuring HCV RNA investigated the association between HCV infection and CHD, the study showed that HCV antibody positivity ($p < 0.001$) and HCV RNA positivity ($p < 0.001$) were independent risk factors for CHD events and that patients with detectable HCV RNA had a significantly higher incidence of CHD events compared to those with only HCV antibody positive but no detectable RNA (5.9% vs. 4.7%, $p = 0.04$).

Moumen [(21)] found that HCV RNA positivity represented an independent predictor of severity coronary artery disease. The mean level of the endothelial biomarker hsCRP was higher in the positive group compared to negative group. In addition, serum GGT level firstly, was significantly increased in HCV RNA positive group. Secondly, it was found to be correlated with number of stenotic vessels and the severity of CAD**.**

A meta-analysis was done by **Olubamwo *et al***. showed that HCV infection may increase the risk of occurrence and the severity of coronary atherosclerosis (as stressed by Gensini score), which seemed consistent with the results of the vast majority of studies evaluating the effect of HCV infection on severity of CAD [(22)]**.**

On the other hand, **Arcari *et al.*** [(17)] found no significant correlation between HCV infection and coronary atherosclerosis, also they found no association between HCV and AMI. This can be attributed to the fact that most MI occured in relation to nonsignificant coronary lesions and to the different pathology of MI from that of SCAD. Similarly **Momiyama *et al.*** [(16)] reported comparable rates of HCV antibody positivity among angiographically documented CAD (at least 50% stenosis in a major coronary artery) patients and controls.

However, there were great differences between these two studies which found no significant correlation between HCV infection and coronary atherosclerosis, and the other studies showed evidence about role of HCV infection in the development of CAD and its severity including the present study.

In contrast, **Arcari *et al.*** [(17)] study was carried out on young active-duty military personnel with mean age of 42.2 who had recent AMI and all patients were males. Also, the study periods were different, which may reflected changing HCV treatment options since the regimen of pegylated-interferon (IFN) alpha and ribavirin was approved

in 2002. Another reason for discripancies in results of different studies may be attributed to varying demographics of patients included in each study, and different genotype of the HCV infection.The way of determination of HCV status (by HCV antibody or by HCV RNA) also may affect the results.

CONCLUSION

The level of HCV RNA detected by quantitative PCR was correlated to the extent and severity of coronary artery disease as assessed by Syntax score in HCV antibody positive patients who were evaluated for CAD by angiogram. The higher the viral load in HCV seropositive patients, suggest greater severity of CHD. Yet it was not found to be significantly correlated to the number of vessels affected. HCV RNA level predicts future cardiovascular risk, The incidence and severity of CAD is much higher in patients with detectable HCV RNA compared with patients with remote infection who are only HCV antibody positive with undetectable HCV RNA.

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