Original Article

CORRELATION OF HEPATITIS C VIRUS INFECTION WITH ANGIOGRAPHIC SEVERITY OF CORONARY ARTERY DISEASE

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ABSTRACT

INTRODUCTION:It is observed that Hepatitis C virus (HCV) infection is associated with high risk of coronary artery disease (CAD), possibly due to increased inflammation.The determination of the large angiographic burden of CAD in HCV infected cases may provide valuable prognostic information.

OBJECTIVES: To find frequency of HCV infection in patients of CAD undergoing coronary angiography and to compare the angiographic burden of CAD in HCV positive and HCV negative patients.

MATERIAL & METHODS: This cross-sectional study was done at Department of Cardiology, Mayo hospital, Lahore from 5th July 2016 to 4th Jan 2017. One hundred and fifty patients planned for coronary angiography were tested for anti-HCV antibodies. All the participants were assessed for presence of conventional risk factors. Angiographic burden of CAD was assessed by using modified Reardon severity scoring system and was compared in patients with and without HCV infection.

RESULTS: In this study, the prevalence of HCV was 27(18%) among 150 patients of CAD undergoing coronary angiography. The mean age of all cases was 52.88±10.44 years whereas mean age in HCV positive and negative cases was 51.59±12.37 years and 53.16±10.00 years respectively. There were 121(80.67%) male and 29(19.33%) female cases in this study. The male to female ratio was 4.17:1. The conventional risk factors like diabetes mellitus, hypertension, family history and dyslipidemia were found to be more common in HCV positive group. The modified Reardon severity score in HCV positive and negative cases was 9.30 ± 2.74 and 7.84±2.66 respectively (p-value < 0.02).

CONCLUSION:The HCV infection in CAD patients undergoing coronary angiography is high i.e. 18% . Coronary risk factors were more frequently seen in HCV positive patients and consequently the angiographic burden of CAD was also high in this group.

KEYWORDS: Hepatitis C Virus, Coronary artery disease, Angiography, modified Reardon severity score

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INTRODUCTION

Ischemic heart disease has high prevalence in our society (6.25%).[1] Ischemic heart disease has a multi-factorial etiology,[2] including increasing age, male gender, lack of physical activity, smoking, diabetes, hypertension, hyperlipidemia and family history as traditional risk factors. However, besides these risk factors, pro-inflammatory state induced by infective agents has long been consider to be associated with enhanced atherosclerosis.[3,4] HCV infection is a viral infection that have been linked with increased incidence of atherosclerosis.[5,6]

The reported seroprevalence of HCV in Pakistan is as high as 5.31%.[7,8] Although liver is the primary target of HCV, it was also isolated from extra-hepatic sites including carotid atheromatous plaques[9] as well as myocardium[10]. Several studies have concluded that HCV infection increases the risk of CAD.[10,11] However, it has not been well studied whether HCV positive patients having CAD, have more severe angiographic burden of CAD as compared to HCV negative patients. Studies have shown contrasting results.[12] In one study, the angiographic burden of CAD was found to be higher in HCV positive patients than HCV negative patients, as assessed by modified Reardon severity score system (8.75±1.69 vs.6.01±1.80, p<0.01),13 while in another study, HCV patients were found to have similar angiographic burden of CADas similar as in HCV-negative patients.[14]

A study done by Vassalle C et al on 491 cases of CAD found that presence of HCV sero-positivity was 6.3% in CAD group.[15] In one local study,[16]

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increased severity of individual coronary artery lesions in HCV positive patients was observed; however, total angiographic burden in HCV positive versus HCV negative patients, calculated by a validated scoring system, has not been studied locally.

The rationale of this study is to address this uncertainty and determine whether HCV positive patients have increased angiographic burden of CAD or not. The determination of the increased angiographic burden of CAD in HCV infected patients may be helpful in providing valuable prognostic information. The results may also help guiding therapy for more aggressive surveillance, adopting prevention strategies and appropriate treatment of CAD in HCV positive patients.

The objective of the study were:

1.To find frequency of HCV infection in patients of CAD undergoing coronary angiography.

2.To compare the angiographic burden of CAD in HCV positive versus negative patients.

MATERIAL & METHODS:

This cross-sectional study was done at Department of Cardiology, Mayo hospital, Lahore from 5th July 2016 to 4th Jan 2017. Sample size 150 was calculated with 95% confidence level, 4% margin of error with anticipated prevalence of HCV infection i.e. 6.3.%[15] in patients of CAD undergoing coronary angiography. A total of 150 patients from both genders, aged 18-70 years, with CAD who gave consent for coronary angiography were included.

Patients with renal failure (GFR < 15 ml/min) , liver failure (AST, ALT >40), severe sepsis (WBC count < 4000 or > 11000/mm^3), advanced malignancy, severe anemia (Hb < 7g/dl) and history of coronary artery bypass grafting (CABG) were excluded.

All the patients planned for coronary angiography due to ischemic heart disease were checked for the presence of anti-HCV antibodies by screening, after obtaining a blood sample of at least 3 ml. Positive results were confirmed by enzyme linked immunosorbent assay (ELISA). All the participants were assessed for the co-existence of conventional risk factors, like family history, smoking, hypertension, diabetes mellitus & hyperlipidaemia. The purpose of study was explain to patients and informed consent was obtained. After coronary angiography, reporting was done by two experienced cardiologists. Angiographic burden of CAD was assessed by calculating modified Reardon severity scoring system[17] and was compared with and without HCV.

Modified Reardon severity score[17]:

The coronary circulation is divided into 8 proximal segments including the left coronary artery, the left anterior descending artery (LAD) to junction of middle & distal 3rd of vessel, proximal 3rd of major septal branch of LAD, proximal 3rd of major diagonal branch of LAD, circumflex coronary artery (CFX) up to the junction of the middle and distal third of the vessel, the proximal third of the major obtuse marginal branch of the CFX, the right coronary artery (RCA) up to and including origin of posterior descending coronary artery (PDA) and proximal 3rd of PDA. Distal vessels are not scored.

Severity of disease is measured by assigning

Luminal narrowing (%)	Severity score
<50	01
50-74	02
75-99	03
100	04

points to each lesion consistent with degree of luminal narrowing. The points for each lesion in proximal coronary circulation are aggregated to get total severity score.

Data entry and analysis was done by using SPSS v22.0. Qualitative data like gender, hepatitis C serology, angiographic burden in of CAD in HCV+ and HCV-group and proportion of patients having established risk factors (hypertension, diabetes, smoking, hyperlipidemia & family history) was expressed as frequency and percentages. Quantitative data like age and modified Reardon severity score (the outcome variable) was expressed as mean ± standard deviation. Data was stratified for age, gender, hypertension, diabetes, smoking, hyperlipidemia & family history to address effect modifiers. Independent samples t-test was applied to compare modified Reardon severity score in HCV positive & Negative cases. P-value ≤0.05 was considered significant.

RESULTS:

In this study the prevalence of HCV was 27(18%) among 150 patients of CAD undergoing coronary angiography.

- The mean age of study population was 52.88±10.44 years whereas mean age in HCV positive and negative cases was 51.59±12.37 years and 53.16±10.00 years. Table-1.

There were 121(80.67%) male and 29(19.33%) female cases in this study. The male-to-female ratio was 4.17:1.

- The modified Reardon severity score in

HCV positive and negative cases was 9.30 ± 2.74 and 7.84±2.66 respectively. The mean modified Reardon severity score was higher significantly in HCV positive cases than HCV negative case, p-value < 0.005. (Table-2)

- There were 46(30.67%) smokers and 104(69.33%) non-smokers.
- There were 42(28%) cases who were diabetics, 28(18.66%) had a positive family history of CAD, 54(36%) cases were hypertensive and hyperlipidemia was diagnosed in 81(54%) of the cases.Both groups were similar with respect to age and gender but frequency of hypertension, smoking, dibetes mellitus, family history of premuture CAD, and dyslipidemia was higher in HCV positive patients. (Table-1)

Table-1: Comparison of baseline characteristics in HCV+ and HCV- Patients

Compared Characteristic*		HCV + (n=27)	HCV – (n=123)
[1]Age	(Mean±SD)	51.59±12.37	53.16±10.00
Gender	[2]Male –n (%)	24 (88)	97 (78)
	[2]Female–n (%)	3 (11)	26 (21%)
[3]Diabetes mellitus-n(%)		21(77)	21(17)
[3]Hypertension–n (%)		24 (88)	30 (24)
[3]Smoking–n (%)		22 (81)	24 (19)
[3]Family History –n (%)		18 (66)	10 (8)
[3]Dyslipidemia –n (%)		24 (88)	57 (46)

*All Fisher's exact tests except for Family History. [1]P=0.481, [2]P=0.291, [3]p < 0.001

Table-2: Comparison of coronary artery disease severity in HCV+ and HCV- Patients

Group	Modified Reardon score (Mean±SD)	*p-value
HCV + (n=27)	9.30±2.74	0.01 - 0.02
HCV - (n=123)	7.84±2.66	

*For equal variance p=.0112 and for unequal it is .016; in either case, it is significant.

Table- 3: Comparison of modified Reardon severity score in positive and negative HCV cases when stratified for age (years)

Age groups		No. of cases	Mean	S.D	p-value
18-50 Years	Positive	10	8.80	2.860	<0.001
	Negative	44	4.70	1.786	
	Total	54	5.46	2.560	
51-70 Years	Positive	17	10.24	3.327	<0.001
	Negative	79	4.70	1.697	
	Total	96	5.68	2.958	

Table- 4: Comparison of modified Reardon severity score in positive and negative HCV cases when stratified for gender

Gender	HCV	Mean	S.D	p-value
Male	Positive (n=24)	9.62	3.360	<0.001
	Negative (n=97)	4.76	1.824	
	Total (n=121)	5.73	2.935	
Female	Positive (n=3)	10.33	1.155	<0.001
	Negative (n=26)	4.46	1.272	
	Total (n=29)	5.07	2.203	

Table- 5: Comparison of modified Reardon severity score in positive and negative HCV cases when stratified for smokers

Smoking	HCV	Mean	S.D	p-value
Yes	Positive (n=22)	9.55	3.501	<0.001
	Negative (n=24)	6.04	2.458	
	Total (n=46)	7.72	3.456	
No	Positive (n=5)	10.40	.894	<0.001
	Negative (n=99)	4.37	1.314	
	Total (n=104)	4.66	1.831	

Table- 6: Comparison of modified Reardon severity score in positive and negative HCV cases when stratified for family history

Family history	HCV	Mean	S.D	p-value
Yes	Positive (n=18)	9.94	3.75	0.001
	Negative (n=10)	5.20	2.25	
	Total (n=28)	8.25	3.99	
No	Positive (n=9)	9.22	1.64	<0.001
	Negative (n=113)	4.65	1.67	
	Total (n=122)	4.99	2.05	

Table- 7: Comparison of modified Reardon severity score in positive and negative HCV cases when stratified for diabetes mellitus

Diabetes mellitus	HCV	Mean	S.D	p-value
Yes	Positive (n=21)	9.57	3.58	<0.001
	Negative (n=21)	4.76	1.84	
	Total (n=42)	7.17	3.72	
No	Positive (n=6)	10.17	0.98	<0.001
	Negative (n=102)	4.69	1.70	
	Total (n=122)	4.99	2.09	

Table- 8: Comparison of modified Reardon severity score in positive and negative HCV cases when stratified for hypertension

Hypertension	HCV	Mean	S.D	p-value
Yes	Positive (n=24)	9.62	3.36	<0.001
	Negative (n=30)	5.57	2.40	
	Total (n=54)	7.37	3.49	
No	Positive (n=3)	10.33	1.15	<0.001
	Negative (n=93)	4.42	1.34	
	Total (n=96)	4.60	1.68	

Table- 9: Comparison of modified Reardon severity score in positive and negative HCV cases when stratified for hyperlipidemia

Hyperlipidemia	HCV	Mean	S.D	p-value
Yes	Positive (n=24)	9.67	3.226	0.097
	Negative (n=57)	4.89	2.024	
	Total (n=81)	6.31	3.266	
No	Positive (n=3)	10.00	3.464	0.088
	Negative (n=66)	4.53	1.406	
	Total (n=69)	4.77	1.872	

- When data was stratified for age groups, gender, smoking, family history, diabetes, hypertension, we found significantly higher mean modified Reardon severity score in HCV positive cases for each stratum, p-value < 0.05. (Tables 3-9)

DISCUSSION:

Atherosclerosis or fat deposition in lumen of coronary arteries is a chronic inflammatory ailment. It is the main clinical indicator for CAD, stroke & ischaemic limbs. The potential role of infectious virus or agent for development of atherosclerosis in rodents, in an experimental trial, was first described>120 years ago[18], and this immune-inflammatory concept gained popularity in recent years[19]. Recently, numerous infectious etiologies for CAD are proposed based on epidemiological relations, but there is no agreement concerning the causative role[20-22]. In recent years, HCV infection has gain attention as having contributing role in development of CAD, but this relationship is not clear completely[5,6]. Few studies showed controversial evidence; some showed no association between HCV infection and CAD[23], while others reported a high risk[15] or an increase in sub-clinical atherosclerosis[24].

HCV+patients have a high risk of developing hepatic steatosis that has several clinical features of metabolic syndrome[25]. Hepatic steatosis is also associated with raised levels of inflammatory markers & endothelial dysfunction. These features propose a naturally plausible phenomena of high risk of CAD in at-least a subgroup of HCV-infected patients[26]. Other clarifications for association between HCV+ and CAD comprise: HCV induced insulin resistance and high risk of metabolic syndrome &diabetes that are also related to cardiovascular risk factors[27]; high number of cases with history of substance abuse & smoking in HCV patients that increase CAD risk [28].

Additionally, it was proposed that HCV colonizes and replicates within carotid plaques,[29] probably cause vascular inflammation. Studies done in healthy individuals found that HCV indicators were associated independently with atherosclerosis[30]. But following researches reported controversial data, some studies approving it while others disagreeing this association[23]. But, latest evidence showed additional cardiovascular death during development of HCV infection. All over the world, the high risk of HCV infection and importance of CAD are the causes of mortality, association of HCV with cardiovascular risk factor requires an extensive research[31].

A study by Vassalle C et al on 491 cases of CAD found that presence of HCV sero-positivity was 6.3% in CAD group[15]. A study in Egypt, where HCV prevalence is high, reported that prevalence of patients with HCV+, undergoing coronary angiography was 30.3%, and among them, HCV+ patients have more severe coronary lesions as compared to non-HCV patients, who underwent coronary angiography[32]. One more study conducted in Taiwan reported that frequency of HCV in patients with Ischemic heart disease was 25.3%.[33] We found that the prevalence of HCV was 27(18%) out of 150 patients of CAD undergoing coronary angiography. In our study, the occurrence of HCV infection was high as compared to prevalence reported by Vassalle et al. However, this prevalence (18%) is much higher as compared to reported HCV prevalence in our general population (5.31%)[7, 8],therefore, it likely points towards a connection between HCV sero-positivity and ischemic heart disease.

A recent statistics showed IHD prevalence was greater among men[34] (7.8%) than women (4.6%).[35] We found that among patients undergoing coronary angiography, there were 121(80.67%) male and 29(19.33%) female cases. The male to female ratio was 4.17:1. Such a huge difference cannot be explained solely on the basis of difference in incidence of ischemic heart disease in both genders. Other possible explanations are neglected healthcare for women as compared to men in general population, under-diagnosis due to atypical presentation in women, and underutilization of coronary angiography in management of ischemic heart disease in women as compared to men, a decision usually taken by doctors and male members of the family, and not the patient herself, due to our social circumstances.

A local cross sectional survey conducted in 2010, reported that the mean age of HCV+ patients was 49.39 ± 12.23 years and HCV- patients were 49.26 ± 9.45 years[16]. We found higher mean age i.e. mean age of all cases was 52.88 ± 10.44 years whereas mean age in HCV positive and negative cases was 51.59 ± 12.37 years and 53.16 ± 10.00 years.

Few recent studies were conducted to objectively evaluate the severity of CAD in HCV patients when controlled for age, gender and race. In two studies, severity of CAD was high in HCV+ patients than HCV- patients, by calculating modified Reardon severity score, the results being 8.75 ± 1.69 vs 6.01 ± 1.80, $p<0.001$, and 6.26 ± 5.39 vs.

2.6 ± 3.03, P < 0.0005[13]. However, a third study did not find significant difference[14]. In this study we found that modified Reardon severity score in HCV positive and negative cases was 9.30 ± 2.74 and 7.84±2.66 respectively. The mean modified Reardon severity score was significantly high in HCV+ cases than HCV- cases, p-value < 0.005. On stratification of data for age groups, gender, smoking, family history, diabetes, hypertension and hyperlipidemia, we found significantly higher mean modified Reardon severity score in HCV positive cases for each stratum, p-value < 0.05. In our study population, all the conventional coronary risk factors were more frequently seen in HCV positive patients. This observation makes the direct effect of HCV infection on genesis of atherosclerotic heart disease doubtful. It is possible that effect of HCV infection on prevalence and severity of coronary artery disease is indirect i.e., by increasing the frequency of well established coronary risk factors.

Insulin resistance[36,37] and diabetes mellitus[36,38] are reported to be more prevalent in patients with chronic HCV infection. Higher prevalence of Hypertension may be related to HCV related renal pathologies like membranoproliferative glomerulonephritis, IgA nephropathy, post-infectious glomerulonephritis, focal and segmental glomerulosclerosis and cryogobulinemic vasculitis[39,40], although patients with significant renal impairment were excluded from this study. Higher frequency of dyslipdemia may be due to high prevalence of diabetes mellitus in HCV+ group. Positive family history was also more prevalent in HCV + patients and it may be incidental or due to clustering of HCV infection itself in the family.

The determination of high angiographic severity of CAD in HCV+ patients may serve to provide valuable prognostic information in these patients. It may also suggest that ischemic heart disease patients should be considered for HCV screening and adopting HCV prevention strategies. These findings may also suggest that HCV positive patients may also be considered for ischemic heart disease surveillance as well as aggressive treatment.

The hypothesis of relationship between HCV infection and severity of CAD has long been controversial. Our findings have put further weight of evidence in favor of this hypothesis. However, this study is limited in its impact due to small sample size. Therefore, further large scale studies should be conducted to confirm these results.

CONCLUSION:

The prevalence of HCV infection in patients with CAD undergoing coronary angiography is high i.e. 18%. The angiographic severity of CAD in HCV positive patients is higher as compared to that in HCV negative patients. Therefore, early screening of ischemic heart disease patients for HCV infection should be considered, and due to increased disease severity, these patients may require aggressive management to reduce further morbidity and mortality and improve overall prognosis.

Author's Contribution

MAA: Collected the data and conducted the study. WA: Consultant incharge of the study. TAB: Helped in conducting the study. AT: Helped in data analysis.

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