Hepatitis C Virus (HCV) "A Possible Independent Risk Factor" for Coronary Artery Disease

Akhtar B.,[1] Hanif A.,[2] Qureshi N.U.S.,[3] Hussain S.,[3] Siddique K.,[4] Khan B.Z.,[5] Bakhshi I.M.[6]
Address for Correspondence: *Assistant Professor, Department of Cardiology, King Edward Medical University Mayo Hospital Lahore, Pakistan*

Background: HCV seropositivity has been linked to the presence of coronary artery disease (CAD).[1] It is reported that HCV infection accelerates atherosclerosis.[2-4] Controversy persists regarding the extent of independent or shared role of HCV infection in the causation of CAD. Therefore we carried out this study to detect the prevalence of CAD among patients with HCV seropositivity.

Objective: To validate the Hypothesis weather HCV seropositivity is associated with CAD or not.

Study Design: Cross – Sectional Analytical type with consecutive sampling of patients with seropositivity for Anti – HCV antibodies. Who were diagnosed just before cardiac catheterization.

Study Place and Period: It was carried out at the department of Cardiology of Mayo Hospital Lahore from January **2006** to December 2008.

Patients and Methods: A total of 273 HCV seropositive patients were in the study group and 195 HCV negative who were age matched and had similar clinical presentation and were admitted at the same institution. All HCV positive patients were confirmed on Eliza. Coronary Angiography was done in all patients.

Results: Mean age of HCV^+ patients was 49.388 ± 12.23 years and HCV^- patients was 49.26 ± 9.45 years. In HCV^+ patients who presented with chest pain, the prevalence of CAD was almost 91% while in HCV^- group it was 78.46%.

Conclusion: Our study has shown an unambiguous and clear association between HCV infection and complex CAD. However these results need to be confirmed in further longitudinal studies.

Key Words: HCV (Hepatitis C – Virus), CHD (Coronary Heart Disease), CAD (Coronary Artery Disease), DM – 2 (Diabetes Mellitus Type – 2), ACS (Acute Coronary Syndrome).

Introduction

Coronary artery disease is the most common form of heart disease with multifactorial etiology. Atherosclerosis being the principal cause. Although, CAD has plaque human kind since ancient days but our knowledge is still limited. Its understanding has much evolved over centuries. Traditionally being viewed as a dyslipidaemic degenerative disease is now considered a dynamic process with strong inflammatory character.[5] The inflammation theory postulates that the initiation and progression of lesions are represented mainly by inflammatory and fibroproliferative process triggered by cytokines and growth factors.[6,7] This inflammatory and oxidative stress may be responsible for progression and destabilization of atherosclerosis plaque and can lead to heart attack, stroke and cardiovascular death. Despite major advances in the diagnosis and treatment of atherosclerosis, our knowledge and understanding are still incomplete. Most of the surveys and studies have focused on specific conventional risk factors (age, sex, Hypertension, DM, Dyslipidemia and smoking). In addition to these traditional atherogenic risk factors, one of the most interesting developments in the recent years has been the idea that infective agents may induce a pro inflammatory effect and have a crucial role in atherothrombosis.[8] At the beginning of the 1970s, the monoclonal hypothesis was proposed which has suggested a potential role for viral infection in the atherosclerotic process.[8,9] In particular, this theory proposed that a mutation or a viral agent may represent events able to transform a single smooth cell into the progenitor of a proliferative clone, introducing the concept that the plaque may be considered a monoclonal benign neoplasm. Since then many additional results have shown an association between infectious agents and atherosclerosis[8,9] although other have produced contrary results.[4] Thus, the role of infections in the pathogenesis of this disease remains controversial. HCV is one of the several viruses which have been linked to the presence of CHD.[10] A positive association between HCV infection and carotid artery plaque has been reported independent from other risk factors for atherosclerosis.[11] HCV infection accelerates atherosclerosis.[11,12] It is associated with elevated cardiovascular risk despite low lipids levels.[13] HCV virus infection and CAD represents a persistent and ever–growing problem in the countries like Pakistan. HCV is a small single stranded RNA virus, identified for the first time in 1989, is a major health care concern worldwide but more so in the developing countries like Pakistan. The reported seroprevalence in Pakistan ranges from 0.7 – 20%. It has already infected more than 10 million people in Pakistan.[14] The

prominent genotype in our country is 3a (75 – 90%).[15] Although liver is primary target of virus infection but most recently blood Leukocytes and myocardium have been reported as possible extra hepatic sites for viral replication.[16,17] Despite the evidence showing a relationship between HCV and atherosclerosis is accumulating any causal link remains tempting but it is not fully proven.[4] In the present study we evaluated whether seropositivity for HCV is associated with CAD or not.

Patients and Methods

Our study population comprised of 273 HCV^+ patients (153 males, 120 females) and 195 HCV^- patients (137 male and 58 females) who were used as a control. Patients selection was according to the previously said criteria. All patients presenting to cardiology department with history of chest pain, cardiac failure and Syncope were admitted in cardiology department at Mayo Hospital Lahore for investigation and treatment. All patients provided written informed consent. All patients gave the complete history which included clinical features, cardiovascular risk factors such as, Hypertension, Diabetes Mellitus, Smoking habits and Dyslipidaemia. All patients had a complete cardiological assessment. Each patient was found to be negative for Hepatitis-B as evaluated by Anti HBS – Ag. Weights and heights were recorded. During the hospital stay electrocardiography, chest radiography, transthorasic echocardiography and abdominal ultrasonography were performed. Blood samples were collected using standard vene puncture technique into groups containing EDTA. Samples were sent for necessary investigations for example, CBC, Serum Transaminases, and Urea Creatinine and for ELIZA analysis of HBS-Ag and Anti – HCV antibodies by a second generation ELIZA technique. Finally Coronary Angiographies were done on all patients by Judkin's technique. Coronary Angiograms were analyzed by expert panel of the cardiologists, independent of other study personnel and without the knowledge of viral status results. Quantitative and Qualitative analysis of Coronary Anatomy was recorded and the data was collected by a specially trained cardiac physician on a specially designed questionnaire which was closed ended and structured.

Statistical Analysis: Data was analyzed by using SPSS 11.5. Mean and Standard error was given for quantitative data. Independent sample t-test was applied to see the significant difference in age, Cholesterol level, HDL and LDL in different binary variables. Chi – square analysis was applied to see the association in qualitative variables (HCV vs. CAD). The Odds ratio (OR) was used to see the magnitude of interdependency between CAD and HCV. A p-value less than 0.05 was consider as significant.

Results

Our study population comprised of 468 (290 males, 178 females). Two hundred and seventy three patients were Anti – HCV Positive (153 male, 120 female) and 195 were Anti – HCV Negative (137 males and 58 females) were used as control and were aged matched and had similar symptoms. The relationship between gender and HCV group was significant (*p – value = 0.001*). The mean age in HCV^- patients was 49.26 ± 9.45 (18 – 76) years and the mean age for HCV+ was 49.88 ± 12.23 (15 – 76) years. The age of patients was independent of gender (*p – value = 0.427*) and HCV (*p – value = 0.561*). Four hundred and four patients (255 HCV^+, 149 HCV^-) belonged to low socioeconomic group while 64 (18 – HCV^+, 46 HCV^-) were middle class. The HCV was dependent of socioeconomic status (*p – value = 0.000).*

Two hundred and ninety six patients (164 HCV^+, 132 HCV) had BMI more than 25 while one hundred and seventy two patients (109 HCV^+ and 63 HCV^-) had BMI less than 25. The status of HCV was also dependent of BMI (*p – value – 0.022*). One hundred sixty six patients (107 HCV^+, 59 HCV^-) were found to be Diabetic. Sixty five patients (60 HCV^+, 5 HCV^-) were recently diagnosed as Diabetic with duration less than one year. The relationship between diabetes and HCV was also significant (*p – value = 0.046*). Hypertension was reported in Two hundred and forty seven patients (142 HCV^+, 105 HCV^-). Eighty four patients had newly diagnosed Hypertension with duration less than 15 months. The relationship between HCV and Hypertension was in-significant (*p – value = 0.448*). History of smoking was present in one hundred and thirty three patients (68 HCV^+, 65 HCV^-). Family history of ischemic heart disease was present in seventy nine patients (37 HCV^+, 42 HCV^-). All were first degree relatives. On lab investigation mean Cholesterol was 179.68 ± 34.5 mg/dl in HCV^+ patients while in HCV^- group it was 198.67 ± 36.70 mg/dl. The cholesterol level was significant with respect to HCV (*p – value = 0.000*).

Mean Triglycerides levels were 160.8 ± 48.151 mg/dl in HCV^+ and 201.06 ± 56.94 mg/dl in HCV^-. The Triglycerides was significantly higher in HCV^- patients (*p – value = 0.000*). The mean HDL level was 38.40 ± 10.3 mg/dl in HCV^+ and 40.22 ± 6.6 mg/dl in HCV^-. LDL levels were 144.26 ± 78.39 mg/dl in HCV^+ and 116.73 ± 32.5 mg/dl in HCV^-. The HDL and LDL was significantly different in HCV (*p – value = 0.015*) and (*p – value = 0.000*) respectively.

ALT and Serum Creatinine levels were raised in 32.23% patients and 13.18% patients respectively. Fatty liver was found in 12.45% patients. On history, ECG and Echocardiography, 222 in HCV^+ group and 194 in HCV^- were with initial clinical diagnosis of ACS. Twenty one patients in HCV^+ group had history of cardiac failure. Nineteen patients had diagnosis of VHD. One patient had diagnosis of ruptured sinus of valsalvae (RSV) while nine patients had diagnosis of complete heart block and one patient had multiple cardiac problems (HF + CHB + ACS). In HCV^- group only one patient had VHD.

In ACS group 354 (85.1%) patients were confirmed on Coronary angiography as CAD patients in which 202 were

HCV $^{+}$ (prevalence = 91%) and 152 were HCV^{-} (prevalence = 78.8%). There was a significant relation between CAD and HCV sero-positivity (*p – value = 0.00*). The presence of HCV enhanced the onset of IHD 2.79 times; the Odds Ratio (OR) was statistically significant (2.791) with *C.I* (1.574, 9.95).

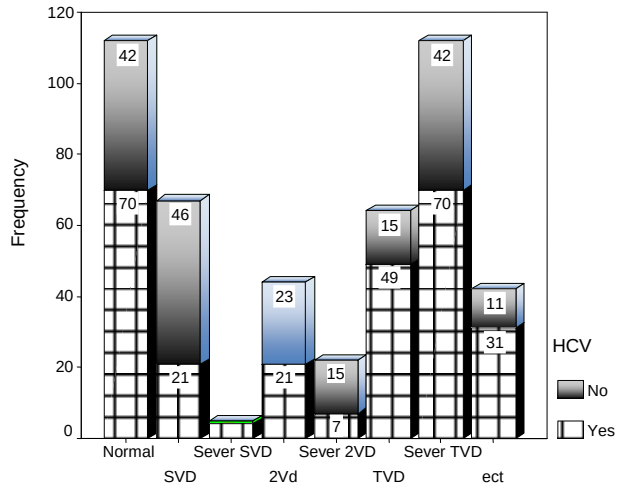
Table 1: *Descriptive Statistics of qualitative base line characteristics in HCV groups.*

		HCV		Total	*p-value*
		+	-		
Gender	Male	153 (32.69%)	137 (29.30%)	290 (61.96%)	***0.001***
	Female	120 (25.64%)	58 (12.40%)	178 (38.0%)	
	Total	**273** (58.33%)	**195** (41.67%)	**468** (100%)	
Socioeconomic status	Poor	255 (54.5%)	149 (31.8%)	255 (54.5%)	***0.000***
	Middle	18 (3.8%)	46 (9.8%)	18 (3.8%)	
	Total	**273** (58.3%)	**195** (41.7%)	**468** (100.0%)	
Diabetes	Yes	107 (22.9%)	59 (12.6%)	166 (35.5%)	***0.046***
	No	166 (35.5%)	136 (29.1%)	302 (64.5%)	
	Total	**273** (58.3%)	**195** (41.7%)	**468** (100%)	
Hypertension	Yes	142 (30.3%)	105 (22.4%)	247 (52.8%)	***0.448***
	No	131 (28.0%)	90 (19.2%)	221 (47.2%)	
	Total	**273** (58.3%)	**195**(41.7%)	**468**(100%)	
Body Mass Index	Under weight	14 (3.0%)	2 (0.4%)	16 (3.4%)	***0.022***
	Normal Weight	95 (20.3%)	61 (13.0%)	156 (33.3%)	
	Over weight	92 (19.7%)	86 (18.4%)	178 (38.0%)	
	Obesity	72 (15.4%)	46 (9.8%)	118 (25.2%)	
	Total	**273** (58.3%)	**195** (41.7%)	**468** (100.0%)	
Smoking	Yes	68 (14.5%)	65 (13.9%)	133 (28.4%)	***0.042***
	No	205 (43.8%)	130 (27.8%)	335 (71.6%)	
	Total	**273** (58.3%)	**195** (41.7%)	**468** (100.0%)	
Family History	Yes	37 (7.9%)	42 (9.0%)	79 (16.9%)	***0.023***
	No	236 (50.4%)	153 (32.7%)	389 (83.1%)	
	Total	**273** (58.3%)	**195** (41.7%)	**468** (100.0%)	
ACS	IHD $^{+}$	202 (48.6%)	152 (36.5%)	354 (85.1%)	***0.000***
	IHD $^{-}$	20 (4.8%)	42 (10.1%)	62 (14.9%)	
	Total	**222** (53.4%)	**194** (40.6%)	**416** (100%)	
		OR= 2.791 (1.574, 9.95) **			

*****The Odds Ratio for ACS Vs HCV is Significant***

Table 2: *Descriptive Statistics of quantitative base line characteristics in HCV groups.*

		HCV		Gender	
		+	-	Male	Female
Age (Years)	**Mean**	49.88 ± 12.23	49.26 ± 9.45	49.945 ± 10.74	49.101 ± 11.78
	Range	15 – 76	20 – 75	18 – 76	15 – 75
	p-value	***0.561***		***0.427***	
Cholesterol (mg/dl)	**Mean**	179.68 ± 34.5	198.67 ± 36.70	183.60 ± 37.24	183.95 ± 33.43
	p-value	***0.000***		***0.757***	
Triglycerides (mg/dl)	**Mean**	160.8 ± 48.151	201.06 ± 56.94	133.61 ± 82.98	139.18 ± 84.13
	p-value	***0.000***		***0.554***	
LDL(mg/dl)	**Mean**	144.26 ± 78.39	116.73 ± 32.5	89.4918 ± 52.03	97.19 ± 103.05
	p-value	***0.15***		***0.382***	
HDL (mg/dl)	**Mean**	38.40 ± 10.3	40.22 ± 6.6	32.05 ± 19.107	29.97 ± 16.19
	p-value	***0.000***		***0.300***	
ALT (mg/dl)	**Mean**	46.16 ± 30.36	Normal	42.47 ± 23.22	50.92 ± 37.21
	Not Applicable			***0.024***	
Creatinine (mg/dl)	**Mean**	1.27 ± 0.69	Normal	1.2354 ± .35	1.3299 ± .97
	Not Applicable			***0.628***	



HCV$^+$ Vs. HCV$^-$

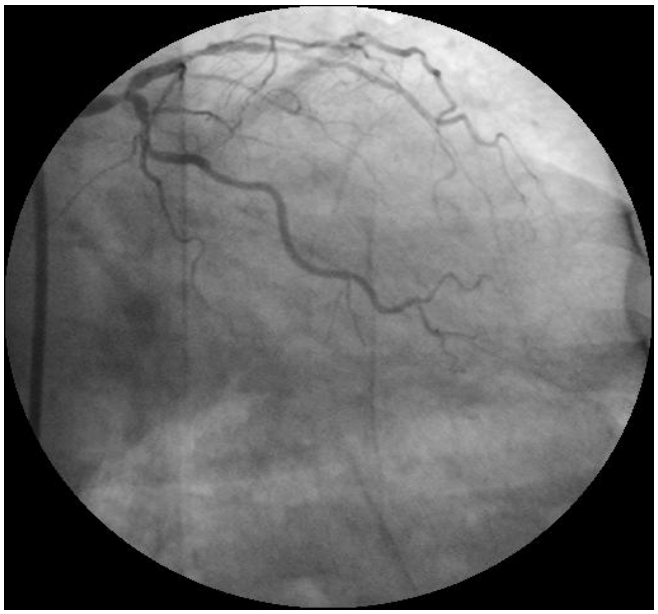
Figure 1: *Distribution of CAD.*

Discussion

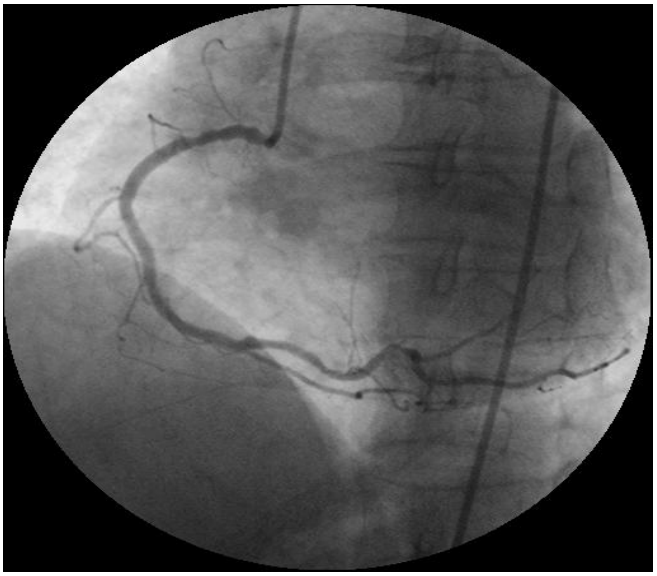
Results in our study have shown a statistically significant difference in gender composition. Overall male population predominated in both the groups but more pronounced in HCV$^-$ group than HCV$^+$ depicting the fact that males are on a higher risk to develop CAD than females. However in our study Anti-HCV$^+$ females had higher prevalence of CHD than HCV$^-$ females and peak occurrence of CAD was at an earlier age (45 years, P – Value = 0.01). While this difference was only marginal in HCV$^+$ male groups (P-Value = 0.05). Mean age of CAD patient was not significant among other sub groups (P – value = 0.48). Four hundred four patients (86.32%) belonged to low socioeconomic status. Among them 255 (54.48%) were HCV$^+$ and the rest were HCV$^-$ 149 (31.84%). Sixty four patients (13.68%), 18 (3.85%) were HCV$^+$ and 46(9.83%) HCV$^-$ in the middle class. Poverty is significantly higher in HCV$^+$ group (P-value = 0.000) explaining the fact that poor socioeconomic status is the cause of causes of CAD.

A few of the most striking findings from the analysis of baseline characteristics were overall higher prevalence of Obesity (BMI > 25 Kg/m^2), Type-2 Diabetes Mellitus especially recent onset and new onset hypertension in HCV$^+$ group. The prevalence of Diabetes in HCV+ group was 39.2% (107 / 273 = 39.2%) and in HCV- group was 29.2% (57 / 195 = 29.2%). Similar observations were made in a number of other studies.[18,19] The reported prevalence of DM – 2 Kwon SY was 46.9%. Patients above 40 years of age have 3.8 folds higher risk to develop DM – 2.[18,19] There

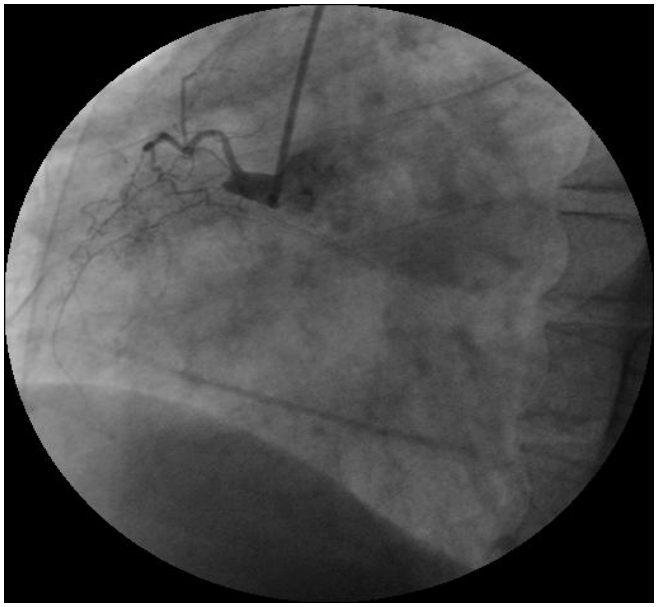
Type of CAD in HCV$^+$ patients



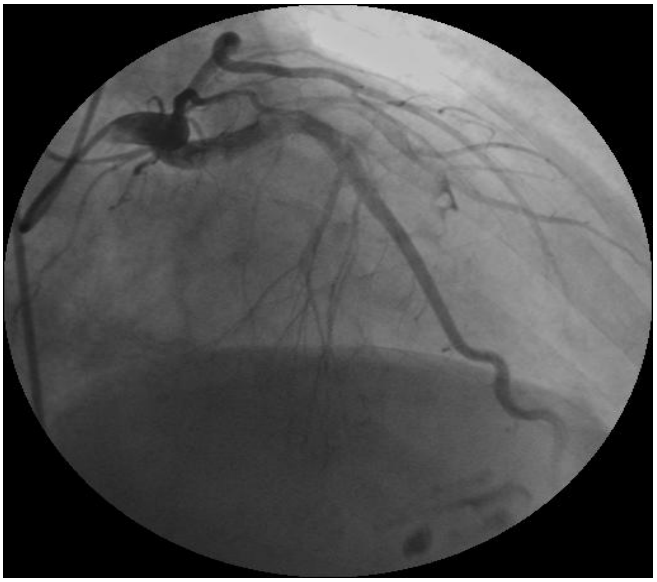
Complex left coronary system disease in HCV$^+$



Complex right coronary system disease in HCV$^+$



Thrombotic right coronary artery occlusion



Sever left system Estatic in HCV $^+$ Patient

was no significant difference between the two groups when frequency of overall Hypertension was considered (P-Value = 0.45, Prevalence of Hypertension in HCV$^+$ was 52.4 (142/273) and in HCV$^-$ it was 53.84% (105/195) but recent onset uncontroll Hypertension was more common in Anti-HCV$^+$ group (79 vs. 5).

An independent role of HCV Cryoglobulinaemia and accelerated Hypertension has been reported by many researchers. It is common and present in majority of the patients at the onset of disease and is often sever and difficult to control.[20-22] Family history of IHD was more frequent in first degree relatives in HCV$^-$ patients (P – value = 0.02) while smoking was more frequent in HCV$^+$ group. Higher prevalence of other athrogenic cardiovascular risk factors has been reported by many others among individuals with Hepatitis C Virus infection.[23] In our study HCV$^+$ patient had significantly low lipids levels than HCV$^-$ group. Similar findings were observed in another study.[13] Our study population with HCV seropositivity had significantly higher frequencies of mildly raised Creatinine, ALT and Fatty liver

changes on abdominal ultrasound. Hepatitis C is known to induce hepatosteatosis responsible for insulin resistance and accelerated atherosclerotic CAD.[20] Prevalence of CAD was not only higher in Anti – HCV+ group (90.2% Vs 78.46) but also had more complex multifarious nature of CAD. Patients had long lesions with osteal involvement and branches of the major vessels. Effected vessels were smaller caliber with more diffusely distributed blockages along with ectasia (P – value = 0.000). Similar nature of CAD is reported by Benditt E et al.[3] According to him advance CAD should be considered as an absolute test and positive assay for Anti – HCV antibodies. Ramdeen N et al, has reported prevalence of Obstructive CAD in patients with chest pain 89% in HCV^+ group Vs. 58% in HCV Sero negative group.[24] Butt A.A has also reported 25% higher risk of CAD in patient with HCV infection despite lower lipid level (P – value < 0.001).[14] The cause of this association is unknown but number of possible mechanisms are reported development of Vasculitis may be either with a direct colonization of the vessel wall by pathogens or stimulation of an inflammatory cascade causing changes in the vessel wall such as thickening, weakening and narrowing leading to Obstructive or Hepatic CAD.[22,8] HCV related Cryoglobulinaemia and immune complex mediated inflammation could be associated with endothelial damage and may account for spontaneous Coronary dissection and acute Coronary Syndrome.[21,25]

In our study after adjustment for other confounding risk factors the Odds ratio has shown that HCV seropositivity still represents and independent predictor of CAD with an OR = 2.79.

Conclusion

Our cross-sectional study has shown an unambiguous and clear association between Hepatitis-C Virus infection complex and advanced CAD. However these results need to be confirmed in further future in longitudinal study.

Suggestions

We should not condone form this awful truth and need a nagging effort to curb HCV spread as even a small lurch from this will be pathetic and will trotter the whole economy.

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