Advanced Research in Gastroenterology & Hepatology
ISSN: 2472-6400

Research Article
Volume 17 Issue 5 - September 2021
DOI: 10.19080/ARGH.2021.17.555971

Adv Res Gastroentero Hepatol

Frequency Distribution of Hepatitis C Virus Genotypes – A Cross Sectional Study

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Submission: September 17, 2021; **Published:** September 27, 2021

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Abstract

Background: Hepatitis C virus (HCV) infection is a common cause of viral hepatitis globally and in Pakistan. The rate of HCV mixed genotype infections is highly variable for different regions and for the same group of patients tested using different HCV genotyping detection methods.

Objectives: To determine the frequency distribution of hepatitis C virus genotypes among patients presenting to a hepatitis clinic in a tertiary care hospital.

Method: A cross-sectional study was conducted in the Hepatitis Clinic of Jinnah hospital Lahore from April – October 2019. A sample of 320 individuals aged between 20-60 years of either gender with hepatitis C for at least the last 6 months were included through non-probability consecutive sampling. About 3 ml of blood sample was drawn with an aseptic technique and sent to the pathology laboratory to determine genotype by PCR. Data were analyzed using SPSS 17.0. Quantitative variables, i.e., age, were summarized as mean and standard deviation, whereas gender and genotype and the presence of mixed genotype were presented as frequency and percentages. Data was stratified for age, gender and duration of hepatitis C for HCV genotyping and post-stratification Chi-square test was applied with p-value < 0.05 taken as statistically significant.

Results: Among 320 patients, 84.4% of respondents were infected with a single serotype, and 11.6% had co-infection with two serotypes. Hepatitis C Genotyping among subjects showed Genotype I was present in 28.8%, Genotype II was in 32.5%, and Genotype III was present in 18.8%. Regarding co-infection, 2.8% were Genotype I &II, 5.9% had Genotype I & III, 1.3% had Genotype I & IV, and Genotype I & VII.

Conclusion: Majority of subjects are infected with single serotype, Co-infection with serotype mostly have Genotype I & III and Genotype I & II.

Keywords: Hepatitis C; Genotype; Co-infection Hepatitis C; Pakistan; Hepatitis C virus; Liver cancer; Hepatitis C virus genotypes; Epidemiology

Introduction

Hepatitis C is the common cause of viral hepatitis globally as well as in Pakistan. World Health Organization (WHO) reported that an estimated 3% of the world's population (170 -200 million people) is chronically infected with hepatitis C virus1. In Asia-Pacific region, the prevalence of chronic hepatitis C ranges from 4% to 12% [1]. In Pakistan more than 12 million people are suffering from HCV that comprise 6% of total population of Pakistan [2] with the highest prevalence of 6.7% hepatitis C reported from Punjab [3]. Hepatitis C virus affects the liver and produces the extrahepatic manifestation of blood, skin, autoimmune, and kidney disease [4].

Hepatitis C virus is an RNA virus that has a high mutation rate resulting in extensive genetic heterogeneity. There are seven genotypes of HCV which were found to be responsible for the disease. However, the literature has shown that humans can be co-infected with more than one genotype (mixed genotype infection) of this virus. The rate of HCV mixed genotype infections is highly variable for different regions and for the same group of patients tested using different assays. Therefore, large variation is seen in the body of the literature reporting the prevalence of mixed infection ranging from 5.5% to as high as 25% [5]. Butt et al. have assessed the burden of mixed genotype infection in patients with hepatitis C and reported it to be 5.5%.6 Aslam et al. [3] addressed the prevalence of Hepatitis C Virus Genotypes in Pakistan, and Bland et al. [6] reported frequency of mixed genotypes in KPK district.

The prevalence of mixed genotype HCV infections has been assessed across numerous geographical regions with broad estimates between 1.2% and 25.3% being reported [7,8]. Although

some variability can be explained by study design differences, populations, and detection methods, the numbers of mixed infection-positive patients identified in studies are frequently low to obtain meaningful statistical power [9]. The incidence of mixed genotype HCV infections in larger studies is less than 8% [9-11]. Data on the prevalence of HCV in Pakistan has previously been comprehensively reviewed [12]. Recent years have seen an increased focus among Pakistani researchers on studying HCV prevalence patterns and frequency distribution of its genotypes. At least eighty-six relevant studies have been published in national and international journals since the reviews mentioned above (2009, 2010). These current studies have not only explored HCV prevalence in previously uncovered areas but have also shed light on the possible connection between underdevelopment and high HCV prevalence (for example, 23.83% prevalence in peri-urban areas of the country's largest city Karachi and 25.1% in rural Sindh [3,13,14]. However, recent years have witnessed an increase in subtype 2a in specific geographical sub-regions within Pakistan. In Khyber Pakhtunkhwa and Sindh provinces, 2a was the second most prevalent genotype (17.3% and 11.3%, respectively). While the changing frequency distribution of various genotypes demands an increased emphasis on research for novel therapeutic regimens, evidence of high nosocomial transmission calls for immediate measures aimed at ensuring safe medical practices [12,15]. Information regarding hepatitis C virus genotypes and subtypes circulating in Pakistan and various risk factors for their transmission is not known well. As genotype determination is crucial for the selection of therapeutic strategies and duration, in such circumstances, there is a need to analyze the HCV genotype distribution pattern in different regions of Pakistan to precisely design a treatment strategy according to viral genotype. Therefore, this study aims to determine the frequency of mixed genotype infections in patients with hepatitis C presenting to at hepatitis clinic of tertiary care hospital.

Methodology

A cross-sectional study was conducted from April – October 2019 in Hepatitis Clinic of Jinnah Hospital Lahore. Total 320 was calculated with a 95% confidence level, 2.5% margin of error, and taking an expected percentage of mixed genotype infection as 5.5%. Patients of both sexes of 20-60 years of age with hepatitis C for at least the last six months were included through non-probability consecutive sampling. Patients of hepatitis C already taking interferon therapy or co-infection with hepatitis B determined by PCR were excluded. After informed consent. About 3ml of blood sample was drawn with an aseptic technique and sent to the pathology laboratory to determine genotype by PCR. Data were analyzed using SPSS 17.0. Quantitative variables, i.e., age, were summarized as mean and standard deviation. In contrast, gender and genotype and the presence of mixed genotype were presented as frequency and percentages. Data was stratified for age, gender, and duration of hepatitis C for HCV genotyping, and post-stratification Chi-square test was applied with p-value < 0.05 taken as statistically significant.

Results

Among 320 individuals mean age was 39.19 + 8.782. 73.1% were males, and 26.9% were females. The mean duration was of Hepatitis C infection was 10.834 + 3.399. 84.4% of respondents were infected with a single serotype, and 11.6% were co-infection with two serotypes (Table 1). Hepatitis C Genotype among subjects showed Genotype I was present in 28.8, Genotype II was in 32.5%, and Genotype III was present in 18.8%. Regarding co-infection, 2.8% were Genotype I &II, 5.9% had Genotype I & III, 1.3% had Genotype I & IV and Genotype I & VII (Figure 1).

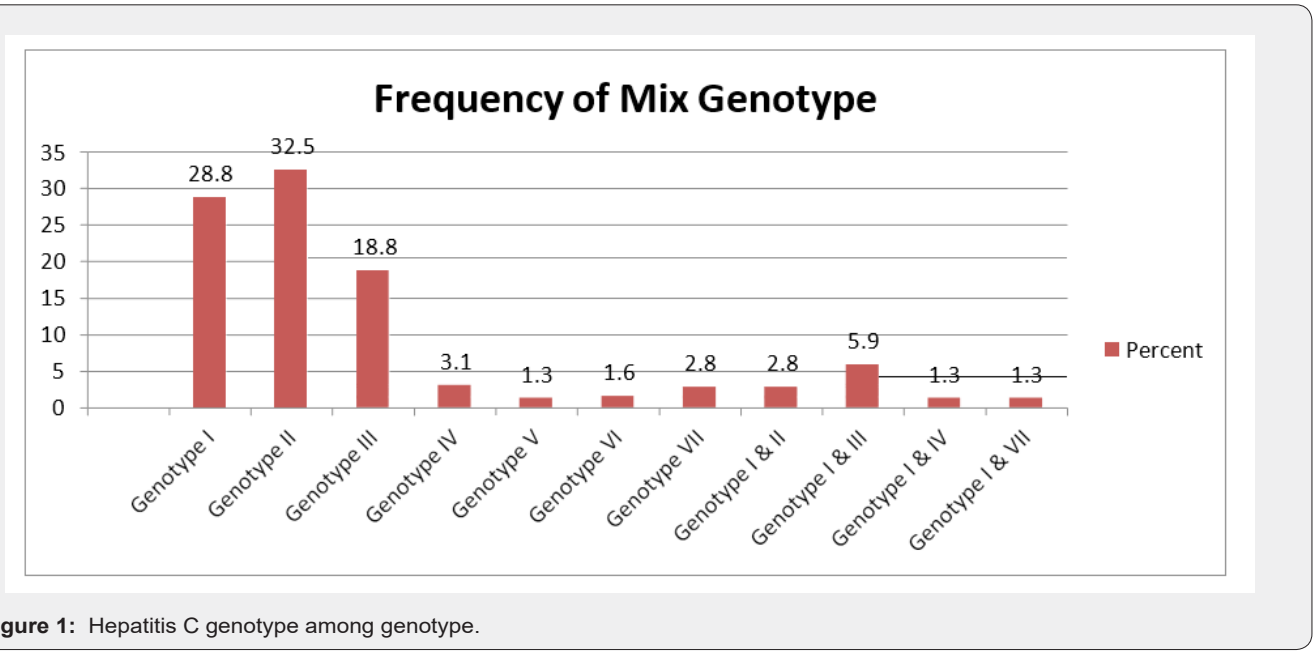

Figure 1: Hepatitis C genotype among genotype.

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Table 1: Demographic and clinical profile of subjects.

Variables (n=320)	Frequency	Percent
Age: Mean=39.19 ± 8.782 Min= 20.00, Max=60.00		
< 40 years	180	56.3
> 40 years	140	43.8
Gender		
Male	234	73.1
Female	86	26.9
Duration infection Mean=10.834 ± 3.399 Min=6, Max=18 years		
< 12 months	241	75.3
> 12 months	79	24.7
Mix Infections		
Yes	37	11.6
No	283	88.4

Mix infection with Hepatitis C was cross tabulated for age, gender, and duration of infection. Among those with co-infection, 10.8% were less than 40 years, and 89.2% were more than 40 years. (X2= 37.320, P =.000). Among those with co-infection, 73.0% were male, and 27.0% were females. (X2= .000, P=.982). Among those with co-infection, 81.1% were less than 12 months of duration, and 18.9% were more than 12 months. The Chi-square test was used to assess significance between age and co-infection and was statistically non-significant. (X2= .749, P =.387 (Table 2).

Table 2: HCV mix infection among age, gender and duration of disease.

Variables Yes		Mix infection Hepatitis C No		Total	Chi-square P value
Age	< 40 years	4	180	184	X^2= 37.320 P value= .000
		10.8%	63.6%	57.5%	
	> 40 years	33	103	136	
		89.2%	36.4%	42.5%	
Gender	Male	27	207	234	X^2= .000 P value= .982
		73.0%	73.1%	73.1%	
	Female	10	76	86	
		27.0%	26.9%	26.9%	
Duration of disease	< 12 months	30	211	241	X^2= .749 P value= .387
		81.1%	74.6%	75.3%	
	> 12 months	7	72	79	
		18.9%	25.4%	24.7%	

Discussion

HCV has come to the top of virus-induced liver diseases in many parts of the world and has gained endemic proportions in our population, but there is no national data collection system for evaluation of genotypes of HCV infection [16,17]. The prevalence of mixed genotype HCV infections has been assessed across numerous geographical regions with broad estimates between 1.2% and 25.3% being reported. Although some variability can be explained by study design differences, populations and detection methods, the numbers of mixed infection positive patients identified in studies are frequently too low to obtain meaningful statistical power [18]. The incidence of mixed genotype HCV infections in larger studies is less than 8%.4-7 In the UK, only a relatively small study has been conducted, which indicated prevalence rates of 9% and 19% in PWID and hemophiliacs, respectively [8]. Many tests currently used in clinical settings lack the sensitivity and specificity required to diagnose mixed infection, which is rarely detected [6,18].

The data on the geographic distribution of genotypes of HCV is among the largest of its kind from Pakistan. Hepatitis C virus

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(HCV) is endemic in Pakistan. Its burden is expected to increase in the coming decades due mainly to the widespread use of unsafe medical procedures. The prevalence of HCV in Pakistan has previously been reviewed. However, the literature search conducted here revealed that at least 86 relevant studies have been produced since the publication of these systematic reviews. A revised updated analysis was therefore needed in order to integrate the new data. A systematic review of data published between 2010 and 2015 showed that HCV seroprevalence among the general adult Pakistani population is 6.8%, while active HCV infection was found in approximately 6% of the population. Studies included in this review have also shown extremely high HCV prevalence in rural and underdeveloped peri-urban [19] areas (up to 25%), highlighting the need for an increased focus on this previously neglected socioeconomic stratum. While a 2.45% seroprevalence among blood donors demands immediate measures to curtail the risk of transfusion-transmitted HCV, a very high prevalence in patients attending hospitals with various non-liver disease-related complaints (up to 30%) suggests a rise in the incidence of nosocomial HCV spread. HCV genotype 3a continues to be the most prevalent subtype infecting people in Pakistan (61.3%). However, recent years have witnessed an increase in the frequency of subtype 2a in specific geographical sub-regions within Pakistan. In KPK and Sindh provinces, 2a was the second most prevalent genotype (17.3% and 11.3%, respectively). While the changing frequency distribution of various genotypes demands an increased emphasis on research for novel therapeutic regimens, evidence of high nosocomial transmission calls for immediate measures aimed at ensuring safe medical practices [6,15,17,18,20].

A study by Attaullah S [17] showed Genotype 1 accounted for 7.03% of the cases, and subtype 1a predominated with a rate of 4.82%. Genotype 2 had a frequency of 3.81%, and the most frequent subtype was 2a (2.89%). Genotype 3 alone contributed to at least 78.96% of all isolates, and the most frequent subtype was 3a (58.01%), followed by 3b (9.76%). Genotypes 4, 5, and 6 were rare, with the rate of 1.59%, 0.10%, and 0.13, respectively. The rates for mixed Genotype and untypeable genotypes were 5.03% and 3.30%. HCV genotypes of mixed infection have been investigated in only 118 (8.25%) individuals and mixed subtypes in 157 (10.98%) individuals. Mixed infection 1&3 was found with the rate of 0.35%, 1&4 (0.003%), 3&6 (0.021%), 2&3 (0.017%), 3&5 (0.007%), 3&4 (0.003%), 1&5 (0.007%) and 2&4&6 (0.007%). The most frequent mixed subtype was 3a&3b (0.387%), followed by 1a&3a (0.06%), 1b&3a (0.05), 1a&3b (0.024%), 2b&3a (0.014%) and 2a&3a (0.010%). (17) In our study, Hepatitis C Genotype among subjects showed Genotype I was present in 28.8, Genotype II was 32.5%, and Genotype III was present in 18.8%. Regarding co-infection, 2.8% were Genotype I &II, 5.9% had Genotype I & III, 1.3% had Genotype I & IV, and Genotype I & VII. 84.4% of respondents were infected with a single serotype, and 11.6% had co-infection with two serotypes.

Conclusion

We concluded that majority of subjects are infected with single serotype, among those with co-infection with serotype mostly have Genotype I & III and Genotype I & II. Co-infection with different serotype is low and mostly prevalent in middle age and among males.

Limitation of Study

A limitation of this study was passive sampling as all the patients presented to the Hepatitis clinic. Our sampling frame included those diagnosed with HCV infection of more than six months. Another limitation was that study findings were representative of a single province study like other studies done in Pakistan.

Future Direction

A population-based seroprevalence study should be conducted in all the country's provinces to evaluate the genotype frequently present and mix genotyping of HCV among our population so that treatment guidelines can further be defined.

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