



A Review of Hepatitis C in the General Population in Pakistan

Pakistan Toplumunda Hepatit C ile İlgili Bir Gözden Geçirme

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ABSTRACT

To perform a systematic review of the recent scientific literature on hepatitis C infection (2010-2016) for epidemiology, genotypes, co-infection, risk factors and management regime in Pakistan. Present integrated, analyzed updated data, a comprehensive effort to evaluate hepatitis C virus (HCV) disease burden in Pakistan, and to inform public health decision makers. Literature search was performed using PubMed, Google Scholar and Scopus from peer-reviewed journals. Criteria for inclusion and exclusion of pooled data with reference to quality and relevance were set prior to meta-analysis. A total of 129 studies were finally included; more than one study on the same region or group of population was included for comparison and statistical authentication. Hepatitis C is endemic in Pakistan with a 40% raise in the incidence of the disease conferring to resent reports. Data of the last five years from different districts of the country show an abrupt elevation in HCV seroprevalence. HCV genotype 3a remains to be the most prevalent in Pakistan (61.3%). However, in recent years, genotype 1a has raised in the Baluchistan province. A significantly high prevalence in transfusion-transmitted diseases is observed. Management of known risk factor can be a significant parameter to control HCV infection. This review encourages further rigorous research efforts to analyze surveillance of HCV in rural remote areas of Pakistan. Furthermore, facilitated access to clinical manifestations should be made to identify risk factors, reduce disease burden and to improve the quality of life of hepatitis C carriers.

Keywords: Hepatitis C, epidemiology, prevalence, genotype distribution, co-infection, transmission

ÖZ

Bu çalışmada Pakistan'da hepatit C enfeksiyonunun epidemiyolojisi, genotipleri, ko-enfeksiyonları, risk faktörleri ve yönetimi konusunda son dönem (2010-2016) bilimsel literatürlerin sistematik bir derlemesi yapılmıştır. Pakistan'daki hepatit C virüsü (HCV) hastalık yükünü değerlendirmek ve halk sağlığı uzmanlarını bilgilendirmek için, kapsamlı bir çalışmayla analiz edilen güncellenmiş veriler günümüze entegre edilmiştir. Literatür araştırmaları PubMed, Google Akademik ve Scopus kullanılarak hakemli dergilerden yapılmıştır. Kalite ve uygunluk için referansla toplanan verilerin dahil edilme ve edilmeme kriterleri meta-analiz için önceden belirlenmiştir. Karşılaştırma ve istatistiksel olarak doğrulama için, benzer bölge veya grup üzerinde birden fazla çalışma, sonuçta toplam 129 çalışma dahil edilmiştir. Güncel raporlara göre insidanda %40 artışla hepatit C Pakistan'da endemiktir. Ülkenin farklı kesimlerinden son 5 yıllık veriler, hepatit C seroprevalansında ani bir yükselişi göstermektedir. HCV 3a genotipi Pakistan'da en yaygın genotip olmaya devam etmektedir. Bununla birlikte son yıllarda genotip 1a Baluchistan eyaletinde artış göstermiştir. Transfüzyonla bulaşan hastalıklarda belirgin olarak yüksek bir prevalans gözlenmiştir. Bilinen risk faktörünün yönetimi HCV enfeksiyonunu kontrol etmek için önemli bir parametre olmalıdır. Bu çalışma Pakistan'ın kırsal bölgelerindeki HCV süreyans analizi için gelecekte yapılacak araştırmaları teşvik edecektir. Ayrıca, risk faktörlerini belirlemek, hastalık yükünü azaltmak ve hepatit C taşıyıcılarının yaşam kalitesini arttırmak için klinik bulguları kolaylaştırmak gerekir.

Anahtar Kelimeler: Hepatit C, epidemiyoloji, prevalans, genotip dağılımı, ko-enfeksiyon, bulaş

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Introduction

Hepatitis C virus (HCV) infection is the most distressing health dilemma worldwide. According to the recent reports of the World Health Organization (WHO), more than 185 million

people of the world are infected with HCV (1). Hepatitis C is a predominant cause of chronic liver complications; one third of the infected patients are predicted to develop steatosis, hepatic cirrhosis or hepatocellular carcinoma (2). Despite of all therapeutic interventions, hepatitis C and its associated causes

are responsible for 350,000 deaths annually (3). Hepatitis C is an asymptomatic infection and the patient remains unaware, but continuous fluctuation in liver enzymes may lead to hepatic injury (4). HCV is more prevalent in developing compared to that in developed countries due to lack of healthcare facilities, poor prognosis and high cost of the available treatments.

Molecular Evolution of Hepatitis C Virus

Choo et al. (4) in 1989, first identified HCV as an enveloped RNA virus. Previously, HCV was named as “non A, non B hepatitis” and was classified as a member of Flaviviridae family (5,6) which also includes Dengue virus. However, the low sequence homology as compared to other flaviviruses eventually led to establishment of new hepacivirus family for HCV (7). There are some other hepatotropic viruses identified as members of hepacivirus family which includes hepatitis A, B, D, E and G (Figure 1) (8).

Genetic sequence of HCV was first characterized in 1989 as highly variable genome with several genotypes which are about 9.6 kb in length (Figure 1) (9). These multiple genomes have high rate of mutation as alteration in sequence that is 1.44×10^{-3} nucleotide per site per annum. Similarly, an evolutionary rate of 7.4×10^{-4} nucleotide replacement per site per annum for E1 gene and 4.1×10^{-4} for the NS5B gene (10) has been identified. Due to this unusual mutational frequency of HCV, development of an effective vaccine is a challenge for scientists and researchers all over the world. How and when HCV was transmitted to human population from Ape species is still a mystery. Moreover, both host and viral factors associated with molecular and cellular mechanism of HCV are not entirely explored. Molecular cloning technique is used for identification and characterization of HCV using blood serum of the infected individual (11). For the confirmation of viremia, initial serological screening is followed by quantitative HCV RNA-based polymerase chain reaction analysis (6). The prime objective of present review was to analyze current epidemiology of HCV infection in Pakistan through comprehensive literature evaluation of the last decade.

Epidemiology

The WHO estimates that more than 3% of the world population (WHO 2014) is living with hepatitis C. Globally, hepatitis C disease burden has a variable geographical distribution whereas, high prevalence is observed in East and Central Asia followed by North Africa and Middle Eastern countries. As larger population resides in the Asian and African regions, the highest prevalence is

observed there as compare to rest of the world (11). Almost 3.7% of Eastern Asia, 3.6% of Middle East and 3.4% of South Asia populations are struggling with hepatitis C (10). The prevalence of HCV infection is estimated at 6% in Pakistan (12), 1.5% in India (13), and 2.2% China (14). However, in underdeveloped countries of Asia, there is lack of authentic data about the disease burden. On the contrary, the developed nations of North America, Western Europe and Australia have low HCV seroprevalence rate i.e. 0.63% in Germany (15), 1% in Canada and 1.1 % in Australia (12). Slightly higher seroprevalence has been reported in some other developed countries like USA (1.7%) (16).

Identification of HCV genotype is critically important for the duration of treatment (17). HCV genotyping is utilized for the production of genotype-specific HCV antibodies. Geographical distribution of genotypes has variable frequency. In West African countries, genetically most diverse genotypes 1 and 2 are more frequent (18). In China and Japan, most HCV infections are due to genotype 1b, whereas genotype 4 is frequently found in Middle East (18) and genotype 5a in South Africa (19). On the other hand, genotype 3a and 1b are more prevalent in Iran, Pakistan and India (20). Patients with HCV genotype 3a are found to be at an accelerated risk of steatosis and hepatic fibrosis whereas, severe liver disease has been reported in patients with chronic HCV genotype 1b (21).

Hepatitis C Prevalence in Pakistan

HCV infection is endemic in Pakistan (22,23,24,25); according to a recent report, the incidence of the disease has increased from 4.7% (41) to 6.8% within a couple of years (28). Unfortunately, low literacy level, inadequate public health facilities and lack of awareness are main reasons behind insufficiency of significant data about the high incidence of the disease in Pakistan. Several studies have reported various HCV infection rates in different geographical areas and ethnic groups in Pakistan (25,26,36,64). In this review, we investigated more than twenty articles on the prevalence of HCV in the country published recently in national and international journals (Table 1).

Majority of the population has never been screened for hepatitis and many individuals have been diagnosed but remained untreated throughout their life. There is no mechanism for the screening of HCV in remote areas and villages of the country where more than 60% of the population is living (68) and ten million people (28,29,30) are reported to have HCV infection. An increase in disease burden is observed in the provinces of Pakistan (31). Data from selected districts of the most populous province Punjab

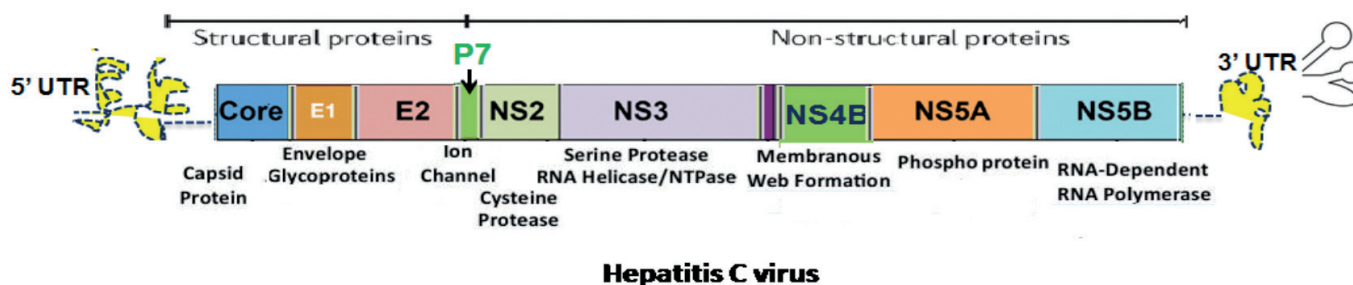


Figure 1. Hepatitis C virus genome

discloses heterogenous results of HCV seroprevalence in recent years. The districts of Punjab include Lahore, Multan, Faisalabad, Gujranwala and Rahimyar Khan (Table 1).

In federal capital Islamabad, the prevalence reported in recent years is 33% in selected group of population. Whereas, studies conducted in different districts of the Khyber Pakhtun Khwa (KPK) province revealed anti-HCV seroprevalence in district Mardan and Mansehra, from Azad Kashmir districts Kotli and Mirpur. Studies of HCV prevalence over the last five years in Sindh Province included the districts of Karachi and Hyderabad. A recent research conducted on HCV frequency in the district of Baluchistan included the provinces of Quetta and Sibi. This review reveals that there are only limited number of studies available in some high prevalence districts, such as Sibi, Mirpur and Kotli. Unfortunately, lack of reports from tribal areas, Gilgit Baltistan, indicates the need for comprehensive studies in these areas (69).

Table 1. Districts wise distribution of anti-hepatitis C virus seroprevalence in Pakistan		
Districts	Anti-HCV seroprevalence	Reference
Islamabad	33%	(32)
Faisalabad	22.68%	(33)
Karachi	6.8%	(34)
Karachi	7.6%	(50)
Multan	3.44%	(35)
Multan	6.68%	(45)
Mardan	64.2%	(37)
Gujranwala	5.16%	(30)
Gujranwala	3%	(35)
Lahore	7.3%	(38)
Faisalabad	21.9%	(29)
Islamabad	23.5%	(40)
Karachi	2.61%	(42)
Lahore	4.9%	(41)
Lahore	15.1%	(73)
Mardan	6.46%	(22)
Quetta	20.8%	(43)
Quetta	8.9%	(45)
Sibi	9.3%	(74)
Mirpur	2.5%	(47)
Kotli	6.38%	(70)
Hyderabad	8%	(33)
Mansehra	7%	(50)
Karachi	25.1%	(51)

Anti-HCV: Anti-hepatitis C virus

Hepatitis C Virus Genotype Distribution Pattern in Pakistan

A comprehensive knowledge of HCV genotypes with reference to the geographical location is often significant for determination of severity and treatment regimen. There are various studies that have established a relationship between genotype and their distribution pattern for better understanding of epidemiological complications (40,41,42,43,44,45). However, genotype determination is an expensive procedure which is carried out by sequencing HCV genome at 5'untranslated region or NS5b region (49). Several research groups have shown that HCV infection genotype 3a is most prevalent in Pakistan, followed by untypeable and 1a genotypes (35,50,52). Whereas untypeable infection remains the second most frequent genotype in population studied (46). Similarly, in this review, all reports have stated the same prevalence order of HCV genotypes in Pakistan (Figure 2). Punjab, the largest province of the country, has been reported to have the highest prevalence of HCV infection (55,56). Similarly, different reports based on data from Sindh and KPK province revealed that genotype 3a and 1a were the most prevalent genotypes, respectively. Pakistan shares its long eastern borders with India where 3a genotype is the most frequent.

However, the data from Baluchistan, geographically the largest province in Pakistan, has shown some variation. According to some studies, genotype 1a, followed by 3a, is predominant in Baluchistan. It is considered that this variation is due to the fact that Iran lies at the western borders of the country. In Iran, 1a is the most frequent genotype (57). Possible shift observed in genotype pattern in KPK is may be due to high mutation or recombination rate in HCV sequence, lack of sensitivity of the present genotyping methods and the migrants from Afghanistan border to tribal regions, and internally displaced people due to war on terror (58). The geographical distribution pattern of HCV genotype is diverse from the rest of the world on the basis of clinical diagnostic methods (59). As untypable, unknown genotypes remain to be second predominant genotype existing in the country. This fact is supported by various studies conducted in Pakistan in the recent years (60,61,62). Therefore, it is a significant challenge for researchers to optimize protocols to sequence the genome of the untypeable genotypes.

Hepatitis C Virus Co-Infections

According to the WHO recommendations, every blood donor should be screened out for at least five transfusion-transmitted

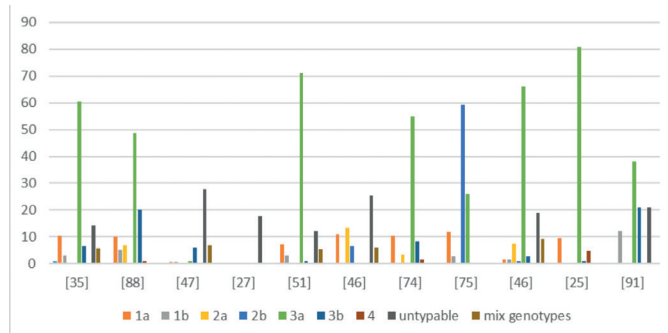


Figure 2. Distribution of hepatitis C virus genotype pattern

infections, such as hepatitis C, hepatitis B, HIV malarial parasite, and syphilis (10). Among donor population, these infectious diseases are the major health concern in developing countries including Pakistan. In case of co-management sound clinical consideration is required to avoid the risks. Limited studies have been conducted in Pakistan which demonstrated an increased rate of co-infection with hepatitis C and hepatitis B virus (HBV), thalassemia and tuberculosis. HBV and HCV co-infection mostly occur in HBV endemic areas, thus, dual infection in Pakistan has been studied by different research groups (64,86,93). Injection drug users (IDU's) have highest rate of HCV and HBV co-infection (69). According to reports from different parts of the country, the prevalence of this co-infection is alarming [0.7% (65) and 3.9% (66)].

Almost 10% of the population of Pakistan is suffering from diabetes mellitus (10). Coexistence of diabetes and HCV infection caused by blood transfusion, surgery, and unsafe insulin syringes is a major health issue. Two studies including data of registered diabetic patients for the screening anti-HCV antibodies has shown the prevalence of 9.3% (68) and 33% (77). Thalassemia is an inherited haemoglobinopathy and the recommended treatment is blood transfusion (70). These transfusions increase the risk of hepatitis C and other transfusion-transmitted diseases if transfusion is made from unscreened donors. According to a study (71), 68.2% of thalassemia patients were screened out for hepatitis C co-infection. During blood transfusion, each time a new, separate syringe can prevent the transmission of HCV in thalassemia patients (72). The frequency of HCV co-infection is illustrated in Figure 3.

Tuberculosis is endemic in regions where blood products are not screened before practice (40). The prevalence of HCV among tuberculosis patients has not been extensively studied in Pakistan (23). HCV and tuberculosis co-infection which increase the risk of liver failure, is 17.02% (67). HIV infection is a serious

life-threatening opportunistic condition. Various reports showed that the incidence of the disease in Pakistan varied between 0.1% (53) and 0.017% (75). Whereas, no subjects were found with HCV and HIV co-infection in other studies (93). The frequency of HCV infection in post-surgery patients in Pakistan is alarming (33). Therefore, pre- and post-surgery serological screening should be performed. Furthermore, the major cause of HCV infection and its co-infections in Pakistan are unsafe blood transfusions (40). In 2003, a comprehensive national blood screening policy was launched (81) as per recommended protocol of WHO. However, in underdeveloped and remote areas of the country, blood screening policy still needs to be implemented for controlling the frequency of transfusion-transmitted diseases.

Modes of Hepatitis C Virus Transmission

HCV infection is intensely associated with imbalance healthcare facilities in different regions of Pakistan. Major causes of transmission are given in Figure 4. There are 12 billion injections administered throughout the world per annum (80), with more than 45% considered unsafe are practiced in African and Asian countries (81,82). Whereas, Pakistan has the highest frequency of therapeutic intramuscular injections per person annually (83). An elevation in HCV infection rates is observed due to IDU's sharing syringes. Drug equipment and unscreened or inadequately screened blood transfusions (85,86). Nevertheless, hepatitis C is proficiently transmitted through transplantation of infected organs and hemodialysis units (87). Various reports on blood donors have shown reduction in hepatitis C frequency through blood transfusions with different prevalence rates such as, 8.34% (20) 7.1% (89) 20.8% (90), which was 68.2% in another study (Figure 4) (71).

A recent research in Pakistan demonstrated that second major risk factor responsible for blood-borne transmission of hepatitis C was occupation. There have been studies showing the prevalence of HCV infection to be varying between 4.13% and 10% among the healthcare workers (90), 38% (91) and 28.10% (92) among barbers, while dental procedures were found to account for 24.54% (94) and 14.2% (99) (Figure 5). In Pakistan, tattooing is least affecting risk factor on contrary to that in the rest of the world. Some of the hepatitis C infection studies conducted on the prevalence among people belonging to different professions showed 3.13% among Punjab Rangers (94), 14.7% in truck

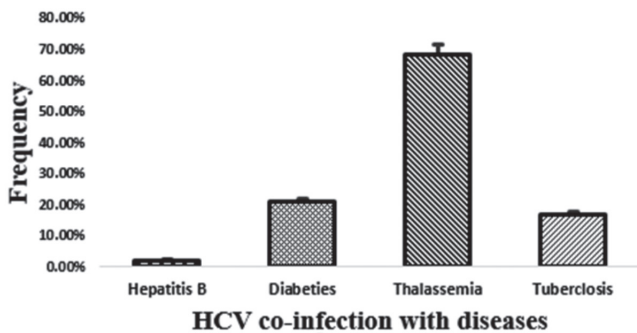


Figure 3. Frequency of hepatitis C infection with hepatitis B, diabetes, thalassemia and tuberculosis
HCV: Hepatitis C virus

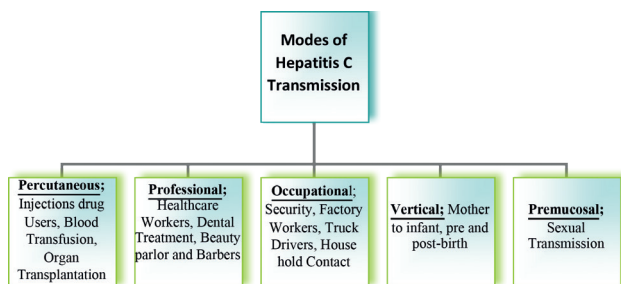


Figure 4. Modes of hepatitis C transmission

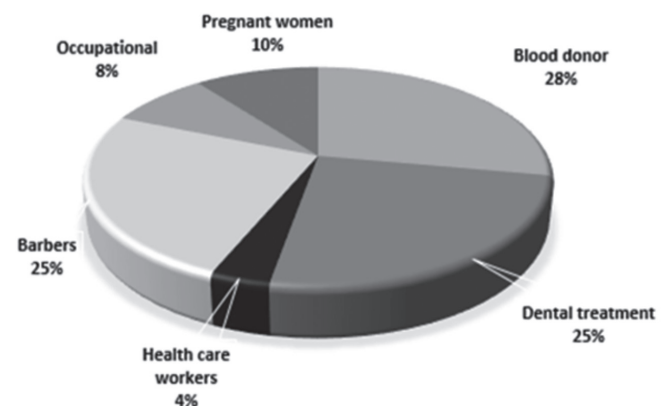


Figure 5. Major risk factors of hepatitis in Pakistan

drivers (95) and 11.38% among factory workers (30). However, it was observed that 36.2% of persons with HCV antibodies were sharing tooth brush, razors, nail cutters and house hold personal belongings (97). Vertical transmission of hepatitis C refers to viral transmission from the mother to the infant. Recently, in a couple of studies, the prevalence of HCV among pregnant women was found to be between 13.3% (98) and 3.45% (99). Viral RNA has been identified in breast milk and colostrum; breast feeding is not a significant risk for mother to infant transmission unless the nipples are intact (100). Even though, HCV RNA has been identified in semen, vaginal fluid, and cervical smears yet, sexual transmission is infrequent (101).

HCV is more frequent among men who have sex with men, heterosexual partners and sex workers (102). Other factors associated with high hepatitis C prevalence comprises of illiteracy, untrained health professionals, and compromised economic background Ford et al. (102). Hence, various awareness programs, basic education and healthcare facilities for all can reduce the prevalence of hepatitis C (104).

Disease Management

With the advances in therapeutic interventions, hepatitis C is curable now and a recovered individual cannot transmit the infection. Previously, the only available therapy was interferon for 6 to 24 weeks (3 million international units) or the same intravenous dose of interferon for 4 to 7 weeks (105). Since 2001, pegylated interferon α with ribavirin has shown favorable results against genotype 2 and 3 (106). Nevertheless, this combination therapy has limited efficacy as well as some adverse effects and low response rate against genotype 1 (107). Currently, for disease management, four new drugs including the protease inhibitors boceprevir, simeprevir, telaprevir are being licensed for HCV genotype 1. A new polymerase inhibitor, sofosbuvir, effective against HCV genotypes 2 and 3 (10), is available on reduced price in Pakistan. These drugs have reduced the risk of hepatocellular carcinoma (107,108). However, telaprevir has been shown to be associated with side effects, such as anemia, rash and pruritus (103,110). This fact emphasizes the inevitability of cost effective, efficient and least toxic hepatitis C therapeutic drugs. Recently, few more HCV inhibitors are at different stages of clinical trials (111).

Conclusion

This systematic review is a pooled analysis to estimate the disease burden attributable to HCV infection. More than 10 million people in Pakistan are suffering from HCV infection, the facts are even worse because there is no data available from remote areas of the country. HCV genotype 3a is the most prevalent genotype in Pakistan. Prediction of genotype assists in selection and time duration of antiviral therapy. Limited studies conducted on HCV co-infections in Pakistan yet their facts and figures are

distressing. Moreover, inadequate healthcare services, illiteracy, high cost prognosis and treatment options are barriers in the way to overcome the high prevalence of HCV infection in Pakistan. Furthermore, comprehensive educational awareness seminars concerning preventive measures and risk factors must be arranged on regular basis for the general population. There is an intense need for the establishment of hepatitis clinical research network and administration of database for HCV screening nationwide.

Ethics

Peer-review: Externally and Internally peer-reviewed.

Authorship Contributions

Concept: Sana Riaz, Atia Iqbal, Design: Sana Riaz, Atia Iqbal, Data Collection or Processing: Sana Riaz, Atia Iqbal, Analysis or Interpretation: Sana Riaz, Atia Iqbal, Literature Search: Sana Riaz, Atia Iqbal, Writing: Sana Riaz, Atia Iqbal.

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