"Prevalence of HCV Co-Infections among High Risk Group and Global Incidence of Hepatocellular Carcinoma"

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Abstract:

Hepatitis is becoming a significant concern in India, serving as a key reason for liver disease in the country. This blood-borne infection poses a high risk of progressing to a chronic state and has linked to hepatocellular carcinoma(HCC), highlighting its critical community health relevance. Transmissions through blood,injecting risk behaviours, high-risk sexual practices among male sex with male (MSM) and unsafe medical procedures involving infected needles are the major cause of hepatitis C virus (HCV) spread, also plays significant role for co-infections. Moreover, addressing risk factors by decreasing high risk behaviour can help to reduce the prevalence. This study determines the current scenario of co-infections in acute and chronic HCV casesamong high risk group (HRG) populations. HCV epidemiology and prevalence among HRGin past few yearswhich includes IDUs, patient undergoing for haemodialysis, MSM, people living in hyper endemic areas, patients with human immunodeficiency virus (HIV), in gender-diverse populations and sex workers. It's a biggest challenge in India that management of HRGand linking them to health care facility, but more cost-effectivetreatment and implement of efficient methods might plays significant role to control the HCV and its associated co-infections.

Keywords: *HCV co-infections, Hepatocellular carcinoma, hepatitis CIndia,HCV co-infection, MSM, IDUs*

Abbreviations used: FHF, fulminanthepatic failure; HCV, hepatitis C virus; HIV, human immunodeficiency virus; STD, sexually transmitted disease; IDU, Intravenous drug user;MSM, Male sex with male; PWID, Persons who inject drugs. HCC, Hepatocellular carcinoma

Background

Hepatitis C virus (HCV) belongs to group Flaviviridae family, genus Hepacivirus. Its infection present in all regions which come under the monitoring of World Health Organization (WHO).[(1)]It's a well-known reason behind liver cirrhosis, the primary reason for liver transplants, and the most

common chronic blood-borne infection in developed countries like United States of America.[2]

The highest burden of disease is in the Eastern Mediterranean Region with 12 million people chronically infected. In the South-East Asia and European Region approximately 9 million peoples are living with HCV followed bythe Western Pacific Region; where 7 million people are infected chronically.[3]Most of the HCV patients in these populations have been chronically infected for many years and no longer take part in risk behaviour.

Hepatitis C epidemiology in India remains insufficiently researched. It was estimated in 2015, approximately 4.7 to 10.9 million people were affected by HCV viremia.[4] but as per a research conducted in 2024 showed only 5.5 million cases are left.[5]In India, with its vast population and diverse socio-economic and cultural landscape, the journey to HCV eradication has presented both obstacles and success narratives.

HCV genotypes and its impact

A notable aspect of the HCV genome is its high genetic variability. Different parts of the genome have various mutation rates, with the E1 and E2 regions being the most variable, while the 5′UTR and terminal 3′UTR have the most conserved sequences.[6]The high mutation rate of RNA viruses is due to the imperfect proofreading capabilities of viral RNA-dependent RNA polymerase's and are unable to rectify error during replication. Consequently, numerous mutants of the parent strain coexist as quasi-species within a single individual.[7] Significant genetic differences across geographical regions allow classification into six primary genotypes. The virus genotype does not seem to affect disease presentation or severity but is a key predictor of the response to antiviral treatment.[8] Research from India indicates a north-south divide, with genotype 3 more common in northern, eastern, and western regions, and genotype 1 more prevalent in southern India. The cause of this phylogenetic difference between the regions remains unexplained.[9,10]

High risk group population in India

In HRG,India has significant flawslikewise, professional blood donation still prevalent despite being condemned by law because paid donors are often driven by financial need, may be more likely to engage in behaviour’s that place them at a higher risk and potentially compromising their health and increasing the risk of infections like HIV and hepatitis, or to conceal these risks during donor screening in order to receive payment.Haemodialysis patients,IDU, frequent blood transfusions, healthcare-related procedures

and social-stigma associated withSTD are some majorissues in the health system and societyare the possiblecause behind the spread of hepatitis C infection.[4,11,12]

Transmission of hepatitis C due to intravenous and percutaneous drug usage is a serious problem in northeast region of India and definitely in the rest of the country as well. A Studyfrom Mizoram,reported an alarming 71.2% HCV prevalence among activeIDUs.[13]

Additional risk groups prone to hepatitis C infection is Jail inmates exhibit a high 5% HCV antibody positivity rate, attributed to high-risk behaviours, IV drug use, and same-gender sexual activity within prisons.[14] Furthermore, patients with kala-azar receive multiple injections, as observed in a Delhi referral hospital thatfemales who received injectable medicines were more susceptible to acquiring HCV infection (26.7% vs. 18.9%) in comparison with overall HCVprevalence,which was (20.6%) in the studied group. Inadequately sterilized needles likely contributed to these patients' infections.[15]

Another major issue in past few years is because of the global COVID-19 pandemic impact, one-year delay in HCV treatment programs could lead to over 72,000 deaths. While specific Indian data are sparse, it is plausible that COVID-19-related lockdowns, travel restrictions, and hospital service redirections affected HCV patient management.[16]

HCV Co-infection with blood borne viruses and other microbes

HIV-HCV

HIV and HCV share transmission pathways, leading to frequent co-infection. The IDUs were in sexually active age group with a risk of infection to their sexual partner. There is high prevalence of HCV and HIV co-infection among IDUs. Prevalence rate of hepatitis C among HIV-infected individuals has varied widely. Study from Department of Microbiology, RIMS, Imphalfound high co-infection rates of 52.4% in IDUs.[17]In another study involved populations with occult HCV infection in HIV positive sexually acquired transmission risk group was 10.3%.[18] Study conducted at a STD clinic of district hospitals in Northern India revealed an HCV sero-prevalence of 1% but they do not find any co-infection positive patient. This might be due to the less number of active male sex with male (MSM) in HIV positive group studied.[19]The HIV epidemic in India is escalating rapidly, with an estimated 2.5 million individuals living with HIV. As a result, hepatitis C is expected to increase its prevalence alongside the HIV epidemic, becoming a significant cause of illness in India.

HBV-HCV

The primary concern with HBV/HCV co-infection is that it can lead to more severe liver disease and an increased risk for progression to liver cancer. The vast majority of those co-infected with HCV and HBV acquired these viruses through IDU, unscreened blood and blood products, or exposure to dirty needles and unsterilized medical equipment. A study conducted in India by Nahid Nahvi*et.al.*illustrated positive results (0.03%) for both hepatitis B and hepatitis C co-infection in patients undergoing surgery and was immune-compromised.[20]According to a study, co-infection of HCV among patients with chronic hepatitis Bvaries from 9% to 30%.[21]

HIV & HBV-HCV

HBV and HCV co-infections in HIV positive individuals is of utmost importance due to the underlying consequences such as the hepatological problems associated with these viruses, which have been shown to decrease the life expectancy in the HIV-infected patients.[22] In a study from North India it was reported that out of 620 HIV positive client's prevalence of dual co-infection of HBV and HCV was found only in 0.16% as illustrated in table 1.[23]

In another study from a city of Uttar Pradesh, India the triple infection was present in 5 (0.317%) patients and out of that 60% are males.[24] All the established studies showed that co-infection of all three life threatening viruses together are reported lesser in South and North India as compared to Western part of India.[25]

Tuberculosis (TB)-HCV

Chronic kidney disease and dialysis patients are at increased risk of acquiring TB-HCV co-infections when compared to the general population. In India high-TB burdens, patients required treatment for both HCV and TB infections simultaneously.[26] A study conducted from Delhi, India showed a case of a young man with a history of intravenous drug abuse, which was diagnosed with disseminated tuberculosis and with a triple infection with HBV, HCV, and HIV.[27]

Syphilis-HBV-HCV

The most prevalent co-infections that affect treatment results and increase early death among individuals living with HIV are syphilis HBV.[28]

In a study conducted by Sunidhi*et. al.,* the prevalence of syphilis, hepatitis B, and hepatitis C was observed in 3.5%, 2%, and 10% of patients, respectively but the prevalence of co-infection was very low and most of the co-infected patients with syphilis, hepatitis B, and/or hepatitis C were

unmarried males belonging to 18–45 years of age group and they had the history of unsafe sexual behaviour.[29]

Co-infections between syphilis and HBV can result in serious consequences and high rates of morbidity and death if they are not identified and treated within time and this will help to control the rate of early death in younger population of India, those who exposed with drug abusers, unsafe sexual practices.[30]

Table-1: Prevalence of co-infection among HRG population [17,20,21,23,24,27,29]

Co-infections	High Risk Group	Prevalence rate
HIV+HCV	IDUs	52.4%
HBV+HCV	History of surgery	0.03%
	Chronic viral Hepatitis	9-30%
HCV+Thallesemia	Genetic disorder	34.6%
HIV+HBV+HCV	Immunocompromised	0.16%
	Elective surgery	0.317%
HBV+HCV+Syphillis	Unsafe sexual behaviour	0.13%
HIV+HBV+HCV+TB	IDU	One case reported till date

HCV epidemiology among HRG

Hepatitis C epidemiology in India is still not well studied. Most prevalence studies focus on blood banks, assuming blood donors mirror the general population. Moreover, the presence of professional donors invalidates this assumption.[31]A Finding from a study conducted by Goel*et.al.* stated that anti-HCV sero-prevalence rate in antenatal cases (ANC) are 0.88% followed by 0.85% in community-based studies and 0.44% in blood donors. It is estimated globally, that HCV infection among pregnant women varies widely between 1-2% depending on geographical location, population demographics, hospitality and risk factors management.[32,33]New infections in India accounted for nearly one-sixth of new infections worldwide, followed by China. Meanwhile India,China and United states had the highest disability-adjusted life years (DALYs) associated with HCV infection.[34]

Data from small and heterogeneous studies on interferon-based treatment showed that the incidence of reinfection after sustained virological response

range from 2-6%among. Persons who inject drugs(PWID) and 10-15%annually among MSM infected with HIV. These differences were mainly due to heterogeneity in study populations with regards to risk behaviours, but also reflect variations in study designs and implemented virological methods.[35]

HCV prevalence in HRG

Population-based studies on prevalence of HCV infection in India are less. Most of the available data are based on blood bank screening, which may not be a reliable indicator of the true infection rate. The data from these studies show wide geographic variations, which may represent a true variation in prevalence due to differences in socio-economic status or cultural and healthcare practices in different regions, or variations in donor populations studied or test kits used for screening.[36]

Large-scale, population-based studies are scarce, yet critical for accurately gauging hepatitis C's health burden in India. Six such studies have been carried out across various Indian regions. Two studies from Andhra Pradesh involved patients from a gastroenterology camp and a Lambada tribal population, showing 1.4% and 2.02% prevalence respectively.[37] In contrast, a smaller Arunachal Pradesh survey showed a much higher 7.89% hepatitis C prevalence.[38] A more extensive rural Maharashtra survey of over 1000 villagers indicated a mere 0.09% HCV infection rate.[39]West Bengal's most comprehensive population-based study used a 1:3 sampling method to select 3579 individuals from 10,737 across nine villages. Among 2973 participants, ELISA identified HCV in 26 individuals (0.71%), but by PCR it was confirmed in 21 cases. The oldest age group (>60 years) exhibited the highest prevalence (1.5%), while those under ten had the lowest (0.31%).[40]

There is a paucity of large population based studies describing the prevalence of hepatitis C in the general population as shown in table 2. These studies give an accurate index of the health burden of hepatitis C in the country. Six such populationbased studies have been reported from various regions in the country.[41,42]

Table 2:HCV prevalence in HRG populations in India

Author	Year	Name of the Journal	Prevalence of HCV co-infections
Ingle R *et al.*	2023	Clinical Epidemiology and Global Health	Out of 26 thalassemia patients, nine (34.6%) tested positive for hepatitis C infection

Anand A *et al.*	2021	Clinical liver Disease	The prevalence rate of antibodies to HCV ranged between 7.2% and 76.6% in patients with HIV
Nahvi N *et al.*	2019	Clinical Epidemiology and Global Health	Only three patients (0.03%) showed positive results for both hepatitis B and hepatitis C co-infection out of 9252
Mohan *et al.*	2018	International Journal of Contemporary Medical Research	Out of 1577 patients admitted for emergency and elective surgery and for conservative treatment, Co-infections were present only in 5 (.317%) patients
Saravanan S *et al*	2007	World Journal of Gastroenterology	Out of the 500 HIV infected participants investigated and 11 (2.2%) HCV positive.
Hussain T *et al.*	2006	International Journal of Infectious Diseases	The prevalence of HCV-HBV co-infection was 0.1%
Singh S *et al.*	2000	International Journal of Infectious Diseases	The prevalence rate of antibodies to HCV is 20.6% in patients with leishmaniasis

Clinical impact of co-infections in HRG population

Patients co-infected with HCV-HIV andHCV-HBV presents a faster progression to liver fibrosis and higher incidence of HCC because these viruses share the same route of transmission.[43]Patients with HIV and liver disease have a higher mortality and the most common etiology are HCV (33%) and HBV (6–10%). In patients with co-infection, liver diseases are the second cause of mortalityafter AIDS.[44]

HCC was more frequent in the patients co-infected with triple infections than in those suffering with mono-infection,some other factors such as; duration of disease, high levels of fibrosis and carbohydrate intolerance might play an important role for the development of HCC.High possibility of HCC in HIV/HCV co-infected patients is due to a lower sustained virologic response and faster progression to fibrosis and cirrhosis.[45]In India viral infections affect the liver more. Patients with co-infection had significantly higher HCV

and HBV viral loads compared to those with HCV alone, suggesting increased disease severity and risk of HCC.[46]

In a study conducted by AwadhAbdullah *et al.*which included 23 studies and conducted the analysis onHCC odds ratio in patients with HBV and HCV co-infectionfound that while only a small percentage of HCV patients were also infected with HBV but co-infection was associated with a significant risk of HCC.Patients with co-infection require continuous monitoring by clinician and testing is required at regular interval for HCV RNA, HBV DNA and other viral and bacterial infections which might be responsible for the critical illness, increases risk of cirrhosis, HCC, and mortality.[47]

Global association of HCC among viral hepatitis co-infection cases

Not only in India has the co-infection with HIV/HCV, HIV/HBV, HBV/HCV and HIV/HBV/HCV but carried significant morbidity globally, due to its higher progression rates to end-stage liver disease or hepatocellular carcinoma (HCC) as illustrated in table 3.[48-58] The higher prevalence reported in India, Italy and Pakistan could be due to their geographical variation.

Table 3:Global incidence of HCC among viral hepatitis co-infection cases

Author	Year of Study	Countries	Co-infection	Total cases	HCC	%
Marconet al.	2018	SOUTHERN BRAZIL	HIV/HCV	79	5	6.32
Luiet al.	2023	CHINA	HIV/HCV	649	50	7.70
Mehershanhiet al.	2022	USA	HIV/HCV	1308	26	1.98
Tassachewet al.	2022	ETHIOPIA	HIV/HCV	128	1	0.78
Chhinaet al.	2020	NORTH INDIA	HIV/HCV	104	22	21.15
Sun *et al.*	2021	US & CANADA	HIV/HCV	9029	5	0.05
Luiet al.	2023	CHINA	HIV/HBV	654	10	1.52
Mehershanhiet al.	2022	USA	HIV/HBV	286	1	0.34
Bittayeet al.	2025	GAMBIA	HIV/HBV	475	17	3.57

Tassachewet al.	2022	ETHIOPIA	HIV/HBV	128	5	3.90
Ikobahet al.	2024	NIGERIA	HIV/HBV	204	4	1.96
Chhinaet al.	2020	NORTH INDIA	HIV/HBV	104	3	2.88
Sun *et al.*	2021	US & CANADA	HIV/HBV	2118	6	0.28
Zampinoet al.	2015	SOUTHERN ITALY	HBV/HCV	56	8	14.28
Iqbalet al.	2025	PAKISTAN	HBV/HCV	348	73	20.97
Vilas *et al.*	2018	KARNATAKA, INDIA	HBV/HCV	3	1	33.33
Luiet al.	2023	CHINA	HIV/HBV/HCV	71	5	7.04
Mehershanhiet al.	2022	USA	HIV/HBV/HCV	124	5	4.03
Chhinaet al.	2020	NORTH INDIA	HIV/HBV/HCV	104	1	0.96
Sun *et al.*	2021	US & CANADA	HIV/HBV/HCV	878	1	0.11

Conclusion

Due to interplay of two or more viruses together it is very difficult to treat patient with co-infections because antiviral treatment is effective against one virus at a time which require adjustments to treatment plans, monitoring for drug interactions, and considering how medications for one infection might affect another. The disease progression of HCC in patients affected with mono or triple co-infection,it becomes very important to understand the role of viral dominance patterns in co-infected individuals and carcinogenetic factors other than viruses, different cultures and habits, prolonged duration of liver disease. Co-infections can result in more severe disease outcomes and higher mortality rates. Besides governmental strategies and financial resources for drug access, testing kits, and operational funds, media involvement to raise public awareness about HCV prevention and treatment options is essential.

Recommendation

To prevent the co-infection from spreading,targeted interventions and region-specific approaches are needed to intervene the heterogeneity of the epidemic of HCV infection. Furthermore, study required to highlights the significance

and impact of Highly Active Antiretroviral Therapy (HAART) on co-infections. Implementation of constructive strategy includes acknowledgement, education and counselling, harm reduction optimization, scaled-up treatment including treatment of injecting networks, post-treatment screening, and rapid retreatment of reinfections. Considering today's need, all peripheral and government hospitals may establish screening facilities, model treatment centre units (MTC) and anti-retroviral centers (ART) with time.

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