A Systematic Review of Risk Factors for Hepatitis C Virus Infection Among Low-Risk Population in India

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Background: **Identification of risk factors for hepatitis C virus (HCV) transmission will help in targeted screening of people who are at risk for HCV.** ***Method:*** **Indian studies, published between January 1989 and June 2020, were systematically reviewed to identify the relevant studies. We searched electronic databases including PubMed/Medline, Embase, Scopus, and Google scholar to identify the original data published in English language. The full-text studies, published in any form, which reported data on risk factors for HCV transmission among low-risk population were selected. The studies which exclusively included high-risk groups were excluded.** ***Results:*** **Data were extracted from 31,176 participants included in 25 studies (median [range] 40 [7–20,113). The participants were HCV infected patients who visited the hospital (n = 10), community population (n = 6), pregnant women (n = 5), blood donors (n = 2), people with diabetes mellitus (n = 1), army recruits (n = 1), or slum dwellers (n = 1). These studies provided data on blood transfusion, use of unsafe injections, minor or major surgery, unsafe dental procedures, tattooing, body piercing, obstetrical procedures, unsafe shaving, intravenous drug use, and unsafe sexual practices as risk factors for HCV transmission.** ***Conclusion:*** **Unsafe injections, body piercing, unsafe dental procedure, unsafe shaving, and tattooing were identified as major risk factors for reported by HCV population participants.More data are needed to identify the risk factors for HCV in Indian population. Risk-factor-targeted screening may increase the yield and reduce the cost of HCV screening in India. (J Clin Exp Hepatol 2022;12:1438–1444)**

Hepatitis C virus (HCV) infection is a treatable cause for chronic hepatitis, cirrhosis and hepatocellular carcinoma. Globally, ~1% population is infected with HCV, more than 71 million need anti-HCV treatment,[1] and more than 399,000 die every year due to HCV-related complication.[2] India along with China, Pakistan, Nigeria, Egypt, and Russia account for more than half of total HCV infections in the world.[3] In India, weighted anti-HCV seroprevalence in low-risk population is close to 0.49%, and the burden is estimated at ~5 million.[4,5]

The direct-acting antiviral (DAA) agents has made a paradigm change in HCV treatment.[6] High safety profile, high (~95%) cure rate, ease of administration, widespread availability, cost-effectiveness of HCV treatment,[7,8] and affordable price of DAAs has led the World Health Organization (WHO) to set the goal to eliminate viral hepatitis by 2030.[9] The Government of India has recently launched National Viral Hepatitis Control Program (NVHCP).

HCV is transmitted through parenteral routes following exposure to contaminated blood/blood products, unsafe needles, unprotected sex, and in utero transmission from mother to child. Specific groups of people, such as those living with HIV (PLHIV), patients on maintenance hemodialysis (MHD), and people who inject drugs (PWID), are known to be at high risk for acquiring HCV infection.

Larger proportion (~88%) of total HCV burden in India are hidden in low-risk general population.[5] The benefit of NVHCP can only be maximized by identification of HCV infection in low-risk population at a preclinical stage. Beyond the universally accepted risk factors for HCV, there could be additional risk factors which might be prevailing in low-risk population. International studies have identified certain unique risk factors in low-risk population, and their identification has shown to improve the yield of HCV screening.[10,11] The cost of universal screening of low-risk population for HCV can be substantially reduced if we could also identify the risk factors for HCV infection among low-risk population in India.

We report the results of our systematic review conducted to identify the risk factors for HCV infection in low-risk population in India.

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Abbreviations: DAA: Direct-acting antivirals; HCV: Hepatitis C virus; MHD: Maintenance hemodialysis; NVHCP: National viral hepatitis control program; PLHIV: People living with HIV; PWID: People who inject drugs; WHO: World Health Organization
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METHODS

Electronic databases including PubMed/Medline, Embase, Scopus, and Google scholar were searched to identify the original data published between January 1989 and June 2020. Detailed search strategy is given as Supplementary file 1. Our search strategy included the various terms used for HCV, name of states, and major cities of the country. Cross-references from the published articles were manullay searched to identify the additional studies, if any.

Inclusion and Exclusion Criteria

We included Indian studies which reported original data on risk factors for HCV transmission among low-risk population, and were published as full-texts in any form such as original article, brief communication, and brief reports. Studies published as abstracts were excluded. We also excluded the studies that exclusively included the participants who are traditionally considered to be at high risk for acquiring HCV such as PLHIV, PWID, men having sex with men, people on MHD, thalassemic or hemophiliac, or high-risk sexual behavior.

Data Extraction

The literature search was performed by AG. Two independent reviewer groups (SP, BB, and AA; and AE and HG) screened the title/abstract to identify the relevant citations. Full-text articles were obtained for the relevant studies satisfying the inclusion criteria. The data were extracted independently by the two groups. Any disagreement between the authors was resolved after discussion with S and AG. Data were extracted from selected studies in a predesigned data extraction form.

RESULTS

Data were extracted from 25 selected studies,[12–36] which provided information from a total of 31,176 participants (Figure 1). Characteristics of the studies included in analysis are summarized in Table 1. The participants, included

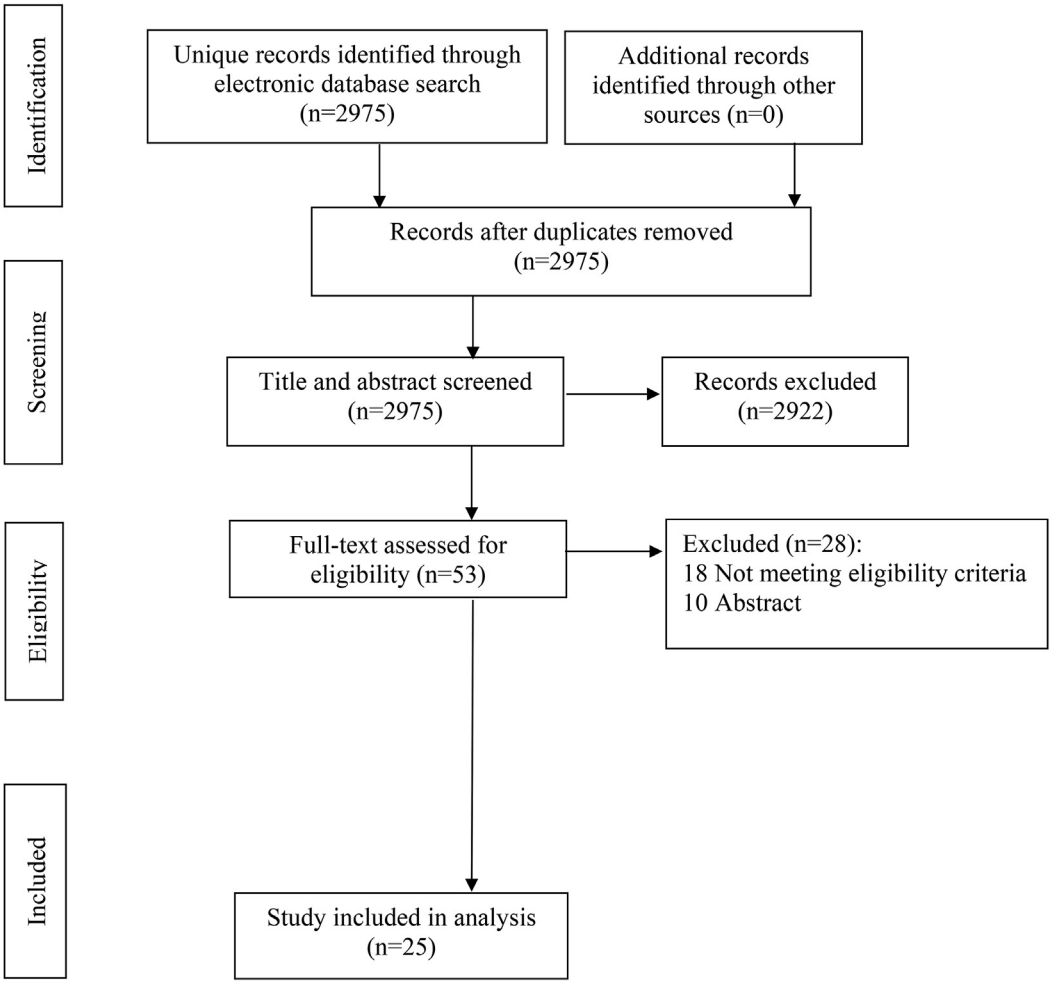

Figure 1 The PRISMA flow diagram for literature search and study selection.

Table 1 Characteristics of the Studies Selected for Analysis.

No	Author, year	State in which study was conducted	Study setting	Study participants (n)	Risk factors studied
1	Khuroo, 1993[12]	Kashmir	Hospital based	HCV positive patients (n = 7)	Unsafe or multiple injections, blood transfusion
2	Sood, 2002[13]	Punjab	Hospital based	HCV positive patients (n = 20)	Unsafe or multiple injections, blood transfusion, major surgery, body piercing
3	Chowdhury, 2003[14]	West Bengal	Community	Community population (n = 26)	Unsafe or multiple injections, dental procedure, tattooing, unsafe shaving
4	Marx, 2003[15]	Tamil Nadu	Community	Slum dwellers (n = 39)	Minor surgery, tattooing
5	Thakral, 2006[16]	Chandigarh	Hospital based	Blood donors (n = 31)	Unsafe or multiple injection, major surgery, unsafe shaving, unsafe sex, intravenous drug use
6	Kumar, 2007[17]	New Delhi	Hospital based	Pregnant women (n = 84)	Blood transfusion, major surgery, body piercing, obstetrical procedure
7	Sharma, 2007[18]	Rajasthan	Hospital based	HCV positive patients (n = 72)	Blood transfusion
8	Parthiban, 2009[19]	Tamil Nadu	Hospital based	Pregnant women (n = 18)	Blood transfusion, unsafe injection or multiple injection
9	Gill, 2010[20]	Punjab	Hospital based	Pregnant women (n = 16)	Blood transfusion, unsafe injection or multiple injection,
10	Singh, 2010[21]	Multi-states	Hospital based	Army Recruit (n = 101)	Intravenous drug use, unsafe sex
11	Medhi, 2012[22]	Assam, Manipur	Hospital based	HCV positive patients (n = 75)	Blood transfusion, intravenous drug use, acupuncture, unsafe sex, unsafe shaving
12	Sood, 2012[23]	Punjab	Hospital based	Pregnant women (n = 7)	Dental procedure
13	Sood, 2012[24]	Punjab	Community	Community population (n = 272)	Blood transfusion, unsafe injection, minor surgery, major surgery, dental procedure, tattooing, body piercing, unsafe sex, intravenous drug use
14	Goyal, 2014[25]	Punjab	Hospital based	Pregnant women (n = 40)	Blood transfusion, major surgery, dental procedure, obstetrical procedures
15	Sharma, 2014[26]	Punjab	Hospital based	Blood donors (n = 49)	Blood transfusion, unsafe injection, major surgery, body piercing, tattooing, intravenous drug use, unsafe sex, unsafe saving practices
16	Vasudevan, 2016[27]	New Delhi	Hospital based	HCV positive patients (n = 211)	Blood transfusion, previous surgery, dental extraction, intravenous drug use, needle stick injury
17	Khatoon, 2017[28]	Uttar Pradesh	Hospital based	HCV positive patients (n = 15)	Blood transfusion, body piercing, intravenous drug use, razor sharing, unsafe sexual activity, major surgery, tattooing
18	Grewal, 2018[29]	Punjab	Hospital based	HCV positive patients (n = 40)	Blood transfusion, unsafe sex, drug addiction, intravenous drug use
19	Gupta, 2018[30]	Punjab	Hospital based	HCV positive patients (n = 740)	Blood transfusion, body piercing, intravenous drug abuse, tattooing, dental procedure, major surgery

Table 1 (*Continued*)

No	Author, year	State in which study was conducted	Study setting	Study participants (n)	Risk factors studied
20	Mahajan, 2018[31]	Punjab	Hospital based	HCV positive patients (n = 8,035)	Dental procedure, unsafe injections, major surgery, blood transfusion, body piercing, intravenous drug use
21	Ramya, 2018[32]	Tamil Nadu	Community	Tribal community (n = 19)	Tattooing, major surgery, unsafe injection, unsafe sex
22	Dhiman, 2019[33]	Punjab	Community	Community population(n = 20,113)	Dental procedure, unsafe injections, major surgery, unprotected sex, tattooing, barber shaving, razor sharing, intravenous drug use
23	Juttada, 2019[34]	Tamil Nadu	Hospital based	People with DM (n = 11)	Major surgery
24	Kar,2019[35]	Odisha	Community	Tribal community (n = 127)	Tattooing, razor sharing, body piercing, unsafe injections, barber shaving,
25	Sood, 2020[36]	Multi-state; 90% participants were from Punjab or Haryana	Hospital based	HCV positive patients (n-1012)	Blood transfusion, Major surgery, Intravenous drug use, Tattooing

DM, Diabetes Mellitus; HCV, Hepatitis C virus

in selected studies, were either known HCV-positive patients (n = 10), community population (n = 6), pregnant women (n = 5), or few other small groups. Only 2 studies had representation of multiple states, 10 studies were from the state of Punjab, remaining 13 studies were from nine states. Of the 37 states/union territories (UTs) in India, only 10 states/UTs were represented in data. The median number of study participant in each study was 40, with minimum being seven and maximum being 20,113.

These studies provided data on blood transfusion, use of unsafe injections, minor or major surgery, unsafe dental procedures, tattooing, body piercing, obstetrical procedures, unsafe shaving, intravenous drug use, and unsafe sexual practices as risk factors for HCV transmission.

The risk factors assessed by different investigators are summarized in Table 2. Among the factors studied, unsafe injections, obstetrical procedures, body piercing, unsafe dental procedure, unsafe shaving, and tattooing were identified as major risk factors reported by HCV population participants.

DISCUSSION

In meta-analysis of risk factors for HCV transmission in India, we observed unsafe injections as the most common cause followed by obstetric procedures and body piercing. Our results have implications for the public health perspective and will be helpful in planning our national policy on HCV screening and case finding.

The successful elimination of viral hepatitis by 2030, as set by WHO, require identification of 90% or more of HCV infected people. Only 20% of those with active HCV infection, progresses to cirrhosis over 20 years[37] while it remains completely asymptomatic in a large proportion. The only measure to identify such subclinical HCV infection in low-risk community population is large-scale screening of the population.

Large-scale screening and linkage with care is one of the major obstacles in HCV elimination. The WHO restricts the HCV screening to individuals who are part of a high-risk population or who have a history of HCV risk exposure or high-risk behavior.[38] The opinion on HCV screening of low-risk community population are divided. The joint guideline of American Association for the Study of Liver Diseases (AASLD) and Infectious Disease Society of America (IDSA) recommend one-time HCV screening[39] for all individuals with age >18 years, whereas European Association for the Study of the Liver (EASL) suggests that optimal regional or national screening approaches should be determined based on the local HCV epidemiology.[40]

The estimated HCV burden in low-risk population in India is ~5 million.[5] As of now, estimated low-risk adult population of India is ~1 billion. Hence, India needs to curate its own HCV screening strategy to identify a large pool of HCV-infected population in a cost-efficient way.

Screening of high-risk population alone will fail to identify 88% of the HCV burden. On the other hand, practice of universal screening will pose not only implementational problem but also a huge financial burden.

Our country needs to adopt a middle way to minimize the cost and maximize the benefits. There could be quite a few screening strategies such as screening of blood and blood product recipients who had received transfusion before the year 2001, that is, before the blood bank screening for HCV was implemented in the country; adoption of passive screening with point of care devices at the time of routine health care; antenatal screening during antenatal visits; or practicing the pre-surgical screening for HCV.

An alternate strategy could be identification of risk factors, associated with HCV transmission in the country, followed by questionnaire-based screening of the low-risk population for their exposures to such risk factors and prioritize their HCV screening. Our review identified blood transfusion, major or minor surgical procedures, dental and obstetric procedures, multiple injections, tattooing, body piercing, and unsafe shaving as risk factors associated with HCV.

The factors reported in our review (multiple injections, obstetrical procedure, tattoo, and dental procedures) are not unique to India. Reports from adjacent countries such as Pakistan[41–43] and Bangladesh,[44] have also identified these factors for HCV transmission. A recent systematic review of thirty studies, from both developed and developing countries, have reported the odd ratio of 1.83 for the risk of HCV transmission with body piercing.[45] Various forms of body piercing, such as Godna, nose piercing, and ear piercing, are very common in Indian culture. These occult routes of transmission might be responsible for HCV transmission among those who lack the traditional risk factors. The identification and screening of these factors might help in self-screening or targeted screening to reduce the cost and increase the yield of investment. Nguyen et al showed in their self-reported 72-item questionnaire that people with two risk factors had a 10% chance of HCV infection, whereas those with ≥4 risk factors had a 50% chance for HCV infection.[46] Another study by Mallette et al reported 7.3% anti-HCV positivity among those who had ≥1 risk factor.[10] In a study from New York tested a 27-item questionnaire in 1000 participants from primary care clinic and reported 8.3% HCV prevalence, which was more than four times the reported national prevalence rate.[11]

The studies, included in our report, had few limitations; first, their results are likely to be influenced by recall bias of the participants because all the participants were aware of their HCV status; second, there were no control groups; third, lack of uniformity in definitions for the reported risk factors; the risk factors were completely based on information provided by the participants but not on documentary evidence; retrospective nature of studies; and identification of risk factors was not the primary objective for any of the studies. Further, we had data from only 10 of the 37 states and UTs in India, with 13 studies from the two states only Punjab[9] and Tamil Nadu.[4] This suggests a gross under representation of the country. The risk factors are likely to vary between the different states in the country.

Although our data had several limitations, the results are important from a public health perspective for the policy makers and primary care physicians. We need to further

Table 2 Risk Factor Studies for Hepatitis C Virus Transmission in India.

Risk factors	No. of studies reported a particular risk factor	Total number of study participants included in studies (N)	Number of participants with a particular risk factor (n)	Proportion of participants with a particular risk factor (%)
Blood transfusion	19	10,778	396	3.7
Unsafe or multiple injections or needle stick injury	14	29,015	15,761	54.3
Minor surgery	2	311	7	2.3
Major surgery	14	30,648	3211	10.5
Unsafe dental procedures	8	29,440	5522	18.8
Tattooing	14	30,582	3496	11.4
Body piercing	9	9373	2393	25.5
Obstetric procedure	2	124	38	30.6
Unsafe shaving	7	20,436	3015	14.7
Intravenous drug user or drug addiction	13	10,647	795	7.5
Unsafe sexual practices	10	20,784	209	1.0

explore the yield of risk-factor-based HCV screening in well-designed prospective studies, preferably in community setting. We can also take measures to reduce the exposure to those risk factors. We can advocate and practice judicious and minimal use of blood and blood products to reduce their unscrupulous use. Similarly, "unsafe shaving practice" shall also be discouraged without blaming any profession or livelihood because reuse of shaving blades and potash alum, a popular astringent in the Indian subcontinent, are presumed to transmit HCV.[47] We shall also educate the health care workers, traditional healers, and traditional dais (lady in the village who provide obstetrical and gynecological services) who frequently perform minor/major surgeries, dental and obstetrical procedures, about the risk of HCV transmission, use of single-use syringes, and biomedical waste disposal.

In conclusion, unsafe injections, dental and obstetrical procedures, previous blood transfusion or surgery, tattooing, body piercing, and unsafe shaving could be a risk factors for HCV transmission in our country, and these risk factors can be used to screen for HCV testing.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Shalimar. Concept, Analysis, First draft; Critical editing**, Sai Priya,** Concept; Study search and selection; First draft**, Hardik Gupta;** Study search and selection; Data extraction; First draft' **Bhavik Bansal;** Study search and selection, Data extraction; Analysis' **Anshuman Elhence;** Study search and selection; Data extraction; First draft**, Ravi V Krishna Kishore;** Data extraction; Analysis; Yes**, Amit Goel;** Concept, Study search and selection, Analysis, Critical editing.

CONFLICTS OF INTEREST

All authors have none to declare.

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AUTHORS' DECLARATION

All the authors had full access to all the data in the study and approves the final version of the manuscript.

ETHICS APPROVAL

Not applicable.

AVAILABILITY OF DATA/MATERIAL

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

CODE AVAILABILITY

Not applicable.

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SUPPLEMENTARY DATA

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