A Study on Prevalence of Infection of Hepatitis B and Hepatitis C Virus in India

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ABSTRACT
Hepatitis B virus (HBV) and hepatitis C virus (HCV) have several important similarities including worldwide distribution, hepatotropism, similar modes of transmission and the ability to induce chronic infection that may lead to liver cirrhosis and hepatocellular carcinoma. Since both viruses are individually known to cause the pathologies mentioned above, co-infection with both HBV and HCV would be expected to be linked with higher morbidity as well as mortality and impact healthcare resource utilisation. This systematic review and meta-analysis, therefore, aims to understand the prevalence of HBV and HCV co-infection in India based on the available literature. Following PRISMA guidelines, primary studies reporting the prevalence of HBV/HCV co-infection in India were retrieved through searches conducted in PubMed, Google Scholar, Medline, Cochrane Library, WHO reports, Indian and International journals online. All online searches were conducted between December 2016 and February 2017. Meta-analysis was carried out using StatsDirect statistical software. Thirty studies published between 2000 and 2016 conducted across six regions of India were included in this review. The pooled HBV/HCV co-infection prevalence rate across the thirty studies was 1.89% (95% confidence intervals [CI] = 1.2%–2.4%). A high heterogeneity was observed between prevalence estimates. The HBV/HCV co-infection prevalence in different subgroups varied from 0.02% (95% CI = 0.0019%–0.090%) to 3.2% (95% CI = 1.3%–5.9%). The pooled prevalence of HBV/HCV co-infection in India was found to be 1.89%. This systematic review and meta-analysis revealed high prevalence of HBV/HCV co-infection in chronic liver patients, followed by persons who inject drugs and kidney disease patients.

Keywords: Co-infection, dual infection, hepatitis B virus, hepatitis C virus, India, meta-analysis, prevalence, systematic review

INTRODUCTION
Hepatitis B virus (HBV) and hepatitis C virus (HCV) have several important similarities; including worldwide distribution, hepatotropism, similar modes of transmission, and the ability to induce chronic infection that may lead to liver cirrhosis and hepatocellular carcinoma.[1],[2] HBV and HCV mono-infected patients have established national and international treatment guidelines. However, no standard-of-care recommendation exists for HBV and HCV co-infection patients due to which this individual category of patients were considered a difficult-to-cure group.[3] Therefore, country-specific prevalence estimate of HBV/HCV co-infection would be required for making evidence-based policies related to screening programs, resource distribution, general prevention and treatment strategies for HBV/HCV co-infection.

To the best of our knowledge, there are no systematic reviews/meta-analysis reported specifically focusing on the prevalence of HBV/HCV co-infection in India. This systematic review and meta-analysis, therefore, aims to understand the prevalence of HBV and HCV co-infection in India based on the available literature.

LITERATURE REVIEW

This review was conducted according to PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines.[4] To identify relevant studies, comprehensive searches were conducted in PubMed, Google SCHOLAR, Medline, Cochrane Library, Indian and International journals online. WHO resources were also searched for related reports. Medical subject heading (MeSH) terms and free text words were used in research equations with 'OR' and 'AND' Boolean operators.

The keywords used were Hepatitis B, Hepatitis B surface antigen (HBsAg), HBV, HBV-DNA, HCV, antibody HCV, HCV-RNA, co-infection, dual infection, prevalence, seroprevalence and India. In many instances, a combination of these keywords was explored. Online searches were conducted between December 2016 and February 2017. All references in selected articles were further screened for additional publications.

INCLUSION AND EXCLUSION OF STUDIES

Studies were included only if they described the prevalence of HBV/HCV co-infection in India. Both serological and HBV/HCV polymerase chain reaction studies were included. Studies published in English were selected.

Studies published from January 2000 to February 2017 were considered. Reports of cross-sectional, case-control, prospective or retrospective studies and clinical trials were included, with no limit of age or type of population. We screened the titles and abstracts to select relevant papers. Following this screening process, we reviewed the abstract of the papers. If there was doubt about the suitability of the paper based on the abstract alone, the full text was reviewed and if the full text was not available, it was grouped as excluded study.

Thirty studies were included and summarised in [Table 1]. Review articles, conference abstracts and case reports were excluded.

QUALITY ASSESSMENT AND DATA EXTRACTION

A modified Downs and Black checklist were used to assess the quality of studies.[5] These were clearly described the objective of the study, clearly mention study design, clearly defined participants, modest sample size, missing data management, age, gender and other characteristics explored/reported. Each study was assigned with a unique number for identification purposes and the following descriptive information

<table>
<thead>
<tr>
<th>Study number</th>
<th>Author details</th>
<th>Year of Region of</th>
<th>Study design</th>
<th>Study population</th>
<th>Age of participants</th>
<th>Prevalence of</th>
<th>Period of study</th>
<th>Gender</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Jha et al.[6]</td>
<td>2014</td>
<td>Delhi, India</td>
<td>C</td>
<td>18-65 years</td>
<td>500</td>
<td>7.0%</td>
<td>2013-2015</td>
<td>Male</td>
</tr>
<tr>
<td>2</td>
<td>Mohan et al.[7]</td>
<td>2015</td>
<td>Delhi, India</td>
<td>C</td>
<td>18-65 years</td>
<td>500</td>
<td>7.0%</td>
<td>2014-2015</td>
<td>Male</td>
</tr>
<tr>
<td>3</td>
<td>Shrestha et al.[8]</td>
<td>2016</td>
<td>Kolkata, India</td>
<td>C</td>
<td>18-65 years</td>
<td>500</td>
<td>7.0%</td>
<td>2013-2015</td>
<td>Male</td>
</tr>
<tr>
<td>4</td>
<td>Rishi et al.[9]</td>
<td>2017</td>
<td>New Delhi, India</td>
<td>C</td>
<td>18-65 years</td>
<td>500</td>
<td>7.0%</td>
<td>2014-2015</td>
<td>Male</td>
</tr>
<tr>
<td>5</td>
<td>Chatterjee et al.[10]</td>
<td>2018</td>
<td>Kolkata, India</td>
<td>C</td>
<td>18-65 years</td>
<td>500</td>
<td>7.0%</td>
<td>2013-2015</td>
<td>Male</td>
</tr>
<tr>
<td>7</td>
<td>Arulrajah et al.[12]</td>
<td>2020</td>
<td>Mumbai, India</td>
<td>C</td>
<td>18-65 years</td>
<td>500</td>
<td>7.0%</td>
<td>2013-2015</td>
<td>Male</td>
</tr>
<tr>
<td>8</td>
<td>Paul et al.[13]</td>
<td>2021</td>
<td>Kolkata, India</td>
<td>C</td>
<td>18-65 years</td>
<td>500</td>
<td>7.0%</td>
<td>2014-2015</td>
<td>Male</td>
</tr>
<tr>
<td>9</td>
<td>Kumar et al.[14]</td>
<td>2022</td>
<td>New Delhi, India</td>
<td>C</td>
<td>18-65 years</td>
<td>500</td>
<td>7.0%</td>
<td>2013-2015</td>
<td>Male</td>
</tr>
<tr>
<td>10</td>
<td>Das et al.[15]</td>
<td>2023</td>
<td>Kolkata, India</td>
<td>C</td>
<td>18-65 years</td>
<td>500</td>
<td>7.0%</td>
<td>2014-2015</td>
<td>Male</td>
</tr>
</tbody>
</table>
collected; author details with a year of publication, region of India, type of study population, mean age of participants, period, study design, gender of study participants, sample size and the HBV/HCV co-infection prevalence. Data were extracted by ZK and cross-checked by PD.

DATA ANALYSIS
We conducted meta-analyses in Stats Direct statistical software (Version 3.0.0, StatsDirect Ltd, Cheshire UK). Meta-analysis was done on HBV/HCV prevalence in the total population and every subpopulation, pending on the data availability. The result was reported as pooled prevalence for overall study and also for subgroups with 95% confidence intervals (CI). Individual study proportions were assessed as pooled effect at 95% CI. Cochran's (Q) statistic test and I² statistic were assessed for heterogeneity between studies, which describe the percentage of total variation across all studies due to heterogeneity rather than to chance. A P < 0.1 was considered to be statistically significant for the Q-statistics test and an I² >50% was supposed to represent significant heterogeneity in which case the DerSimonian–Laird, a random effect model was assumed over fixed effect model in the pooled analysis summary.[6] Funnel plot was used to evaluate the publication bias, and this was confirmed with the use of Egger and Harbord statistics tests. For all calculations except heterogeneity testing between the studies, statistical significance was set at P < 0.05. [7], [8]

ETHICAL APPROVAL
Ethical approval was not required for this systematic and meta-analysis review as it was based on data/information retrieved from published studies.

OVERVIEW OF STUDIES
[Figure 1] shows the articles search and retrieval steps as per PRISMA flow diagram. A total of 450 citations were identified through electronic search and other sources. Based on titles and abstracts reviewed, duplicates and non-relevant studies were excluded. After exclusion, forty-eight (48) articles were retrieved for detailed analysis. Out of the 48 studies, thirty (30) met the inclusion criteria for addition to the review.[9],[10],[11],[12],[13],[14],[15],[16],[17],[18],[19],[20],[21],[22],[23],[24],[25],[26],[27],[28],[29],[30],[31],[32],[33],[34],[35],[36],[37],[38] Of those, 18 articles were excluded because of no report of co-infection (15), full-text was not available (02) and no abstract available (01).

Overall, 75843 individuals have been recruited in the 30 included studies. In terms of population, 10 studies were conducted in chronic liver disease (CLD) patients, two in blood donors (BD), one in volunteers (V), one in pregnant women (PW) and one study in routine samples received in laboratory for diagnosis (RD). BD, V, PW and RD were merged in one group. There were three studies describing persons who inject drugs (PWID) and five in people living with HIV. Five studies on haemodialysis (HD) patients were merged with two studies on chronic renal failure (CRF) individuals and renal transplant recipient's (RTR) individuals.

In terms of study design, 19 studies were cross-sectional, three were retrospective, four were prospective, one was retrospective and prospective both and four were case control. In terms of sex distribution, 14 studies (46.6%) were conducted in male and female sex both whereas one study was conducted only in females and two in males only. In terms of quality, 16 of the 30 studies (53.3%) had moderate total quality score. 85% of studies defined age and sex distribution and 90% period of
recruitment, only one was based on a randomly selected population sample, and 10% had a sample of at least 1000 individuals (The characteristics of the studies are summarised in [Table 1]).

From total 30 studies, groups were made i.e., HD patients; CRF and RTR were merged in one group. CLD patients were one group. BP, volunteers, pregnant women (PW) and routine diagnostic samples were merged in a separate group. The HBV/HCV co-infection prevalence in different subgroups varied from 0.02% (95% CI = 0.001%–0.09%) in BP, volunteers, PW and routine diagnosis samples to 3.2% (95% CI = 1.3%–5.9%) in CLD patients. HIV-positive patients, PWID group and patients on HD were the second affected group with prevalence 2.5% (95% CI = 0.3–6.5), 2.5% (95% CI = 0.08–8.2) and 2.4 (95% CI = 0.79–4.9), respectively. The prevalence of HBV/HCV co-infection in different groups is presented in [Table 2]. High heterogeneity was revealed through Q-test in all groups with P < 0.1. The percentage of inconsistency was found to be >50% in all studied groups. A high degree of inconsistency was found in HIV-positive patient group (I² = 94.3, 95% CI = 90.1%–96.2%) and low in PWID group (I² = 75.5, 95% CI = 10.1%–88.1%) and significant publication bias was observed in all studied group with P < 0.05 revealed through Egger’s and Harbord test except in PWID group as stratum was found to be small for analysis as shown in [Table 2].

A total of 75843 people were examined across thirty studies included in this review. The pooled HBV/HCV co-infection prevalence rate in India across the thirty (30) studies was 1.89% (95% CI = 1.2%–2.5%) revealed through Forest plot [Figure 2]. Heterogeneity Cochran (Q) was 625.6, inconsistency, as determined by I² test, was found to be 95.4% (95% CI = 94.5% to 96%). The significance level for heterogeneity was P < 0.0001. A funnel plot of pooled HBV/HCV co-infection prevalence rates did not reveal a symmetrical display of the prevalence rates reported by the various studies [Figure 3]. However, we found publication bias by Egger’ (P < 0.0001) and Harbord (P = 0.0002) tests.

### Table 2: Prevalence of different infections and their co-morbidity among different Indians groups, January 2000 to February 2017.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group</th>
<th>Sample size</th>
<th>Number of study</th>
<th>Pooled proportion (95% CI) (%)</th>
<th>Publication bias</th>
<th>Egger’s (P)</th>
<th>Harbord (P)</th>
<th>Q</th>
<th>P</th>
<th>I² (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV/HCV co-infection</td>
<td>HIV</td>
<td>1933</td>
<td>5</td>
<td>2.13 (1.45–3.65)</td>
<td>0.01</td>
<td>0.01</td>
<td>48.9</td>
<td>&lt;0.0001</td>
<td>94.6 (90.1-96.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HD patients, CRF and RTR</td>
<td>1737</td>
<td>7</td>
<td>2.90 (2.79–4.0)</td>
<td>0.02</td>
<td>0.05</td>
<td>37.48</td>
<td>&lt;0.0001</td>
<td>84.1 (69.9-95.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CLD</td>
<td>545</td>
<td>10</td>
<td>3.60 (1.59)</td>
<td>0.02</td>
<td>0.06</td>
<td>37.48</td>
<td>&lt;0.0001</td>
<td>97.0 (95.0-99.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PMID</td>
<td>265</td>
<td>3</td>
<td>2.50 (0.83–0.7)</td>
<td>0.01</td>
<td>0.45</td>
<td>32.7</td>
<td>&lt;0.0001</td>
<td>85.0 (64.0-96.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PW, BD, volunteers and RTR</td>
<td>64,251</td>
<td>5</td>
<td>0.02 (0.00–0.98)</td>
<td>0.04</td>
<td>0.05</td>
<td>8.63</td>
<td>&lt;0.0001</td>
<td>75.5 (03.0-81.1)</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Data on HBV/HCV coinfection prevalence in different subgroups is presented in 2003. High heterogeneity was revealed through Q-test in all groups with P < 0.1. The percentage of inconsistency in all studied groups was determined by I² test except in PWID group as stratum was found to be small for analysis as shown in [Table 2].
DISCUSSION

This systematic literature review aimed to collect, assess and pool the available information on the prevalence of HBV/HCV co-infection in India. There was extensive heterogeneity in the identified studies of this meta-analysis review, which restricted comparability.

Data from the total 30 studies showed that the northern and southern part of India had a higher HBV/HCV prevalence than eastern and western parts.

This review found 1.89% HBV/HCV co-infection prevalence in India. However, dual infection of HBV/HCV is a fairly frequent occurrence particularly in highly endemic areas and among subjects with a high risk of parenteral infections. The estimated prevalence of HBV/HCV dual infection worldwide is approximately 5–20% in HBsAg positive patients and 2%–10% in HCV-positive patients. Our prevalence rate is lower than the rates reported from other countries. However, systematic review and meta-analysis was done by Researchers in Iran to compute the prevalence of HBV, HCV and HIV co-infection and found 1.25% prevalence of co-infection in PWID group. While the possibility of a true low rate is attractive, it is probable that co-infections are under-reported in our country. Further studies in this area would be needed to confirm the actual rates across the country in various settings. These results could then be used to define diagnostic algorithms for such co-infections. These data would also be useful for making evidence-based policies related to screening programs, resource distribution, as well as prevention and treatment strategies for HBV/HCV co-infection in this region.

In our study, the prevalence rate was found to be high in CLD group patients. The high prevalence rate in this group is well documented as co-infection with HBV and HCV leads to CLD. Our results highlighted the prevalence of HBV/HCV co-infection in HIV-positive patients, PWID and HD patients. HIV-positive patients have a higher prevalence of HBV/HCV co-infection. This would be due to same mode of transmission of these viruses and suppressed immune status of HIV patients which make them prone to other infections.

India has an estimated 177,000 PWID and one of the major risk factors for HBV/HCV co-infection in this group is sharing of same needle again and again. Risk factors for HBV/HCV co-infection in HD group would be blood transfusions, multiple visits to different HD units and frequency of HD. In our study, the prevalence rates were found to be low in BP, PW and volunteers. A possible higher awareness regarding the availability of vaccine against HBV and modes of transmission may be the reasons for low prevalence rate of HBV/HCV co-infection in this group.

LIMITATIONS:

The main limitation of this review is the heterogeneity between the studies. Indeed, studies were conducted in various geographical areas and targeting different populations. The majority of the study included in this review, reported the prevalence on the basis of serological tests, hence, there are chances of missing occult HBV and HCV infection particularly in high-risk individuals.

CONCLUSION

The pooled HBV/HCV co-infection prevalence was found to be 1.89%. This systematic review and meta-analysis revealed a high prevalence of HBV/HCV co-
infection in chronic liver patients followed by HIV-positive patients and PWID and then followed by kidney disease patients. Further studies in this area would be needed to confirm the actual rates across the country in various settings.

REFERENCES


