Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(3), 79-87 | ISSN:2251-6727

Prevalence of Oral Manifestations in Hepatitis C Virus (HCV) Infected Patients: A Systematic Review and Meta-Analysis

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(Received: 16 March 2025 Revised: 20 April 2025 Accepted: 01 May2025)

KEYWORDS

HCV infections, extrahepatic manifestations, oral lesions, systematic review, meta-analysis

ABSTRACT:

Introduction: Hepatitis C virus (HCV) infection is a chronic viral disease that primarily affects the liver, potentially leading to severe complications such as cirrhosis and hepatocellular carcinoma. Early detection of HCV is challenging due to its often-asymptomatic nature, with diagnosis relying on serological tests. Extrahepatic manifestations, including oral symptoms, can aid in diagnosis and provide insights into the broader impact of the disease.

Objectives: This systematic review aims to assess the frequency of occurrence of oral manifestations in cases positive for HCV infection.

Methods: A systematic search was conducted across three databases (PubMed, EBSCO, Cochrane) from 1st January 2000 to 31st December 2023 to identify studies published in English that reported oral symptoms in HCV-positive patients. The review was conducted following the PRISMA guidelines, and the risk of bias was assessed using the Joanna Briggs Institute appraisal tool. Statistical analyses were performed using n Meta XL version 5.1 with 95% confidence intervals (CI) and 95% prediction intervals for future prevalence estimates.

Results: After a 2-step selection process, 17 studies were included. Overall, 1666 patients from 9 countries were assessed. Sjogren's syndrome was the most common oral manifestation, with a pooled prevalence of 26%. The pooled prevalence for xerostomia was 23%, for recurrent aphthous ulcers was 13%, 11% for oral lichen planus, 10% for candidiasis and 7% for oral leukoplakia. Gingivitis, periodontitis, angular cheilitis and pigmentation were other reported oral manifestations in HCV positive patients.

Conclusions: Since extra hepatic manifestations of HCV are not uncommon and the disease is known to persist in a subclinical course, educating the healthcare professionals and patients regarding the same, may improve the oral healthcare and reduce the outcome related burden of the disease.

1. Introduction

Hepatitis C virus (HCV) infection is a chronic viral infection attacking primarily the liver, leading to inflammation and chronic potentially lethal sequelae, like liver cirrhosis and hepatocarcinoma.[1] HCV is a single-stranded, encapsulated, positive sense RNA virus with a diameter of 50 nm that replicates in hepatocytes and peripheral blood mononuclear cells.[2] According to World Health Organization (WHO), there are over 58 million HCV infections worldwide, with approximately 1.5 million new cases annually and 290,000 deaths from HCV infection.[3] The highest prevalence of HCV infection is in Egypt (11.9%) with genotype 4 being its most common variant.[4] In India, the estimated number of people living with active HCV

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JCHR (2025) 15(3), 79-87 | ISSN:2251-6727

infection ranges from 10 to 24 million, whereas the estimated seroprevalence of HCV among the healthy population is between 0.09 and 2.02%.[5] Risk of HCV transmission is reported to be 1.8%.[6] The primary route of transmission of the virus is parenteral with the highest incidence among people with repeated direct percutaneous exposures.[7]

Due to the subtle nature of HCV infection, only 20% of patients with the virus receive a diagnosis, and only 15% of those with a diagnosis receive treatment.[3] Approximately 74% of patients with hepatitis C will have HCV-related extra-hepatic manifestations of some severity in their lifetime, possibly as a result of viral infiltration of tissues or immunological trigger mechanisms.[8] The extra-hepatic manifestations of HCV infection can involve oral, nervous, renal, gastrointestinal, muscular systems, bones and skin.[9]

The impact of HCV infection on oral health has received different opinions over time. Studies show higher prevalence of oral manifestations in HCV infection (83.3%) as compared to healthy individuals (16.67%). Some of the most frequently reported extrahepatic manifestations of HCV infection involving the oral region predominantly are oral lichen planus (OLP), sialadenitis, Sjogrens syndrome, candidiasis and xerostomia. [4]

2. Objectives

The prevalence of these manifestations varies from place to place due to the changes in viral, genetic and environmental factors. These manifestations are not only a cause of morbidity, but also serves as an indicator to the underlying disease. Early diagnosis can aid in initiation of therapy by healthcare professionals thus preventing further transmission of the disease.

Thus, the aim of this study was to assess the frequency of occurrence of oral manifestations in cases positive for HCV infection.

3. Methods

Protocol and registration

This systematic review and meta-analysis was performed in accordance with Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA 2020) [10] statement guidelines, the Cochrane Handbook for systematic reviews of interventions version 5.1.0. [11] The Cochrane Collaboration, and is registered at PROSPERO under the registration code, **CRD42024498228**. The population, intervention/condition, control/comparison, and outcome (PICO) strategy was used to frame a research question. The following focused question was proposed "-What is the prevalence of oral manifestations in hepatitis c virus infected patients?"

Search strategy:

The review follows the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for 2020. Using keywords and MeSH terms, we formed a search strategy and used it to conduct searches on databases. A comprehensive literature search was made on PubMed, Cochrane and EBSCO databases from January 2000 to December 2023. Seventeen (17) articles were selected which met the inclusion criteria, of which, 09 were cohort, 03 were case-control studies and 05 were cross-sectional studies.

Screening and selection of studies

Two reviewers, independently undertook a three-step selection of studies in the databases based on eligibility criteria. In 1st step, the titles of the articles were screened and irrelevant articles were excluded. The second step included the screening of remaining articles based on the abstract, and the third step screened articles after reading the full text to verify the degree of compliance that the studies had, with eligibility criteria, and make a final decision of their inclusion in this review.

Systematic Literature Search and Selection Criteria

Inclusion criteria:

1. Studies published between 1/1/2000 to 31/12/2023.
2. Studies published in English language.
3. Studies assessing mucocutaneous manifestations in patients with HCV infection.
4. Studies where patients are under anti-viral therapy for HCV infections.
5. Studies with full-text articles only were included.

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6. Studies restricted to patients with HCV infections having mucocutaneous manifestations.
7. Observational studies including case-control, cross-sectional, prospective and retrospective studies.

Exclusion criteria:

1. Studies not fully available in the database.
2. Literature reviews, case reports, case series, surveys and systematic reviews.
3. In-vitro and animal studies or studies including lesions with other viral co-infections.
4. Studies where patients are under anti-viral therapy for any infections other than HCV.
5. Full text articles mentioned in languages other than English to avoid any misinterpretation of the results written in other languages.

Data extraction

Data was extracted from the full published articles for each study and was collected in a Microsoft excel worksheet. Age/gender and oral manifestations were recorded.

Statistical Analysis for Quantitative Synthesis

Pooled estimates of the prevalence of oral diseases among patients suffering from Hepatitis C infection in population-based studies were calculated using the random-effects meta-analysis model, due to the anticipated heterogeneity that results from the difference in methodological approach, geographical location, diagnostic criteria, data sources and geographic settings. Statistical analyses were performed using n Meta XL version 5.1 with 95% confidence intervals (CI) and 95% prediction intervals for future prevalence estimates. The Freeman–Tukey double-arcsine transformation was used for variance stabilization of proportions before pooling the data with the random-effects model. Chi-square and Tau-square were used to assess whether the observed difference was homogeneous or heterogeneous among the studies. Heterogeneity was assessed using I 2 with thresholds of ≥25%, ≥50% and ≥75% indicating low, moderate and high heterogeneity, respectively.

4. Results

A comprehensive search generated 331 articles. This included 158 from Pubmed, 118 from Cochrane and 55 from EBSCO databases. After removing the duplicates, 03 studies were eliminated and 329 studies were selected. 2 reviewers independently screened the Title and Abstract. They subsequently consented that 31 studies should be retrieved for detailed review. 17 relevant studies were eligible for inclusion after full text evaluation and applying strict inclusion and exclusion criteria with a sample size of 1845 HCV infected patients.

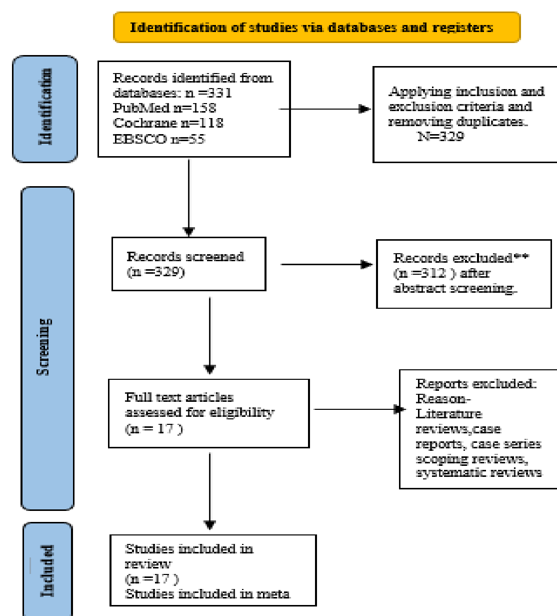

Figure 1: Prisma flowchart

Pooled prevalence of oral manifestations in HCV infected patients are:

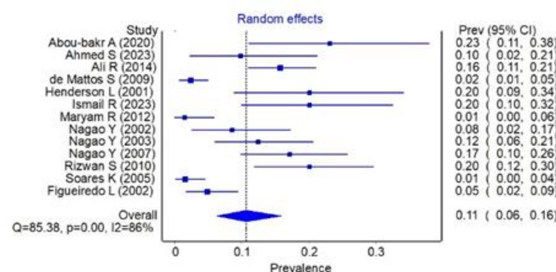

Figure 2: Forest plots of oral lichen planus among the patients suffering from Hepatitis C infection, using rectangles to represent point estimates of each study and diamonds for the pooled estimate from 13 studies using random effect model. The pooled prevalence of oral lichen planus 11% (P, 11%, 95% CI = 6%- 16%, I^2- 86%).

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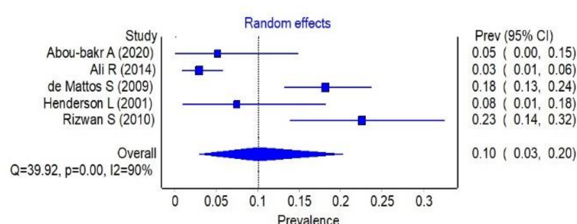

Figure 3: Forest plots of candidiasis among the patients suffering from Hepatitis C infection, using rectangles to represent point estimates of each study and diamonds for the pooled estimate from 5 studies using random effect model. The pooled prevalence of candidiasis among the patients suffering from Hepatitis C infection 10% (P, 10%, 95% CI = 3%- 20%, I^2- 90%).

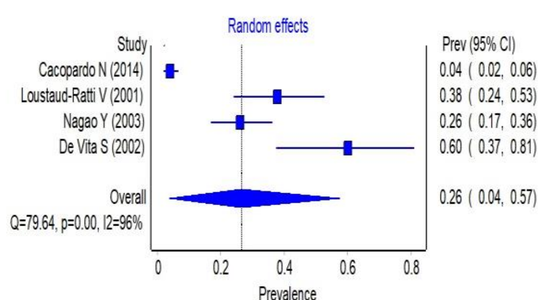

Figure 4: Forest plots of Sjogren syndrome among the patients suffering from Hepatitis C infection, using rectangles to represent point estimates of each study and diamonds for the pooled estimate from 4 studies using random effect model. The pooled prevalence of Sjogren syndrome among the patients suffering from Hepatitis C infection 26% (P, 26%, 95% CI = 4%-57%, I^2- 96%).

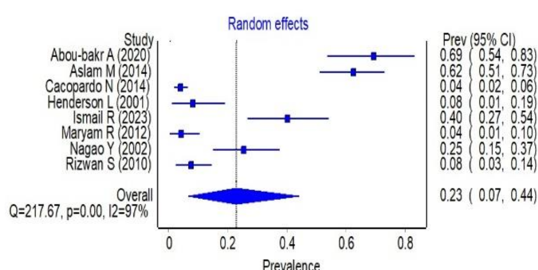

Figure 5: Forest plots of xerostomia among the patients suffering from Hepatitis C infection, using rectangles to represent point estimates of each study and diamonds for the pooled estimate from 8 studies using random effect model. The pooled prevalence of xerostomia among the patients suffering from Hepatitis C infection 23% (P, 23%, 95% CI = 7%- 44%, I^2- 97%).

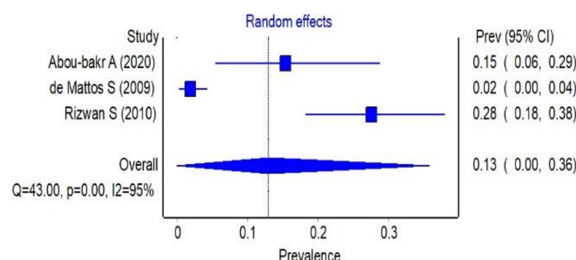

Figure 6: Forest plots of recurrent aphthous ulcer among the patients suffering from Hepatitis C infection, using rectangles to represent point estimates of each study and diamonds for the pooled estimate from 3 studies using random effect model. The pooled prevalence of recurrent aphthous ulcer among the patients suffering from Hepatitis C infection 13% (P, 13%, 95% CI = 0%- 53%, I^2- 36%).

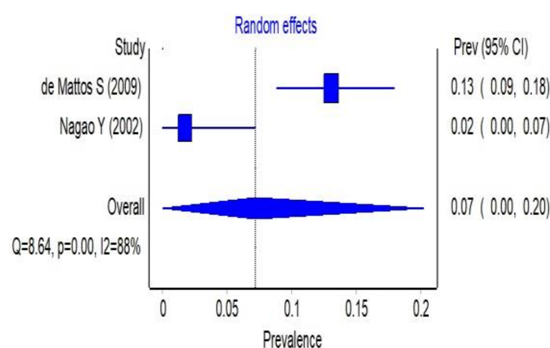

Figure 7: Forest plots of leukoplakia among the patients suffering from Hepatitis C infection, using rectangles to represent point estimates of each study and diamonds for the pooled estimate from 2 studies using random effect model. The pooled prevalence of leucoplakia among the patients suffering from Hepatitis C infection 7% (P, 7%, 95% CI = 0%- 20%, I^2- 88%).

Risk of Bias Assessment

The critical appraisal tool, recommended by the **Joanna Briggs Institute (JBI)** was used to assess the risk of bias of the chosen articles. [25] Only one study was considered to be of low risk of bias. Other all studies were considered as high risk. Three parameters

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were not met by most studies: (1) appropriate sample size estimation (2) appropriate statistical analysis; and (3) study subjects.

When analysing published the studies, most common oral manifestations reported related to HCV infection were Sjogren's syndrome, xerostomia, recurrent aphthous ulcer, oral lichen planus, candidiasis and leukoplakia, that pose challenges in dental practice. Mean age of patients with HCV infection was 56 years.

Discussion

Dental practitioners can play a major role in the early diagnosis and referral of affected patients and hence prevent the disease transmission. The review attempts to explain the association between various oral manifestations and HCV infection. The actual prevalence of the oral manifestations is underestimated due to the lack of proper oral examination and documentation in these patients.

The most frequent oral manifestations observed among the patients with HCV infection is Sjogren's syndrome (SS) (pooled prevalence = 26%). The first study reporting an association between salivary gland disorders and hepatitis C published in 1992 by **Haddad J et al** revealed that 57% of HCV- associated chronic liver disease patients exhibited characteristic SS histological changes in the salivary glands.[26] **Cacopardo B et al** in their study observed the prevalence of Sjogren's syndrome in HCV infected patients to be 22.7% on the basis of persistent xerostomia and xerophtalmia, positive Schirmer's test, positive anti-SSA/SSB antibodies and diffuse dishomogeneity at imaging procedures.[14] Similarly a study conducted in Japan revealed that the prevalence of Sjogren syndrome to be 25.9% according to European criteria and 21% according to Japanese criteria which was higher than the prevalence of Sjogren's syndrome in HBV infected patients.[2]

Different mechanisms may participate in the pathogenesis of HCV-associated SS. Possible explanations include direct infection and proliferation of HCV in salivary glands, molecular mimicry between HCV and salivary glands and formation of immune complexes containing HCV. In contrast to SS, lymphocytic infiltration in HCV+ve cases was pericapillary rather than periductal, with no destruction of the salivary gland ducts, and lymphocytic capillaritis resembled an early stage of disease. [2] **Smyth et al.** indicated that DQB1*02 was significantly associated with viral persistence. [27] According to the American European classification criteria for SS, the presence of HCV is considered an exclusion criterion, this strongly pointing out that sialadenitis in HCV-positive patients is clearly different from SS. [26] Haddad et al found SS histological changes in the salivary glands in 57% of HCV- associated chronic liver disease patients.[30] Also it is to be noted that in some studies, patients were not shown to have SS until they were subjected to salivary and lachrymal function tests and serological examination due to absence of any subjective symptoms.[2]

The pooled prevalence of xerostomia in this study was found to be 23%. In a study conducted by **Abou Bakr A et al** in 2020 to evaluate the oral health status of the HCV infected cases, the prevalence of xerostomia was found to be 69.2% which did not show any statistical significance when compared to the control group.[12] This was in contrast to another study conducted in Egypt where the presence of HCV was significantly associated with increased odds of xerostomia.[4] Also a study on oral health evaluation of HCV infected patients observed that xerostomia was present in 7.5% of patients. The results demonstrated a significantly reduced salivary flow rate for the study group, compared with healthy controls. [16]

The higher incidence of xerostomia in HCV infected patients may be attributed to evasion of HCV to salivary glands causing both sialadenitis and Sjogren like Syndrome or interferon and ribavirin therapy.[13] Direct infection and proliferation of HCV and salivary glands and formation of immune complexes containing HCV also may contribute to the pathogenesis.[14] Also deficiency in salivary flow may be contributed to various other oral manifestations as candidiasis, difficulty in chewing and talking, dental caries and altered taste. [4]

The pooled prevalence of RAU among HCV infected individuals was 13%. **Abou Bakr A et** al in 2020 in their study evaluated and compared the oral health status, of patients with and without HCV infection and found the prevalence of recurrent aphthous ulcer to be 15.4% in HCV positive cases which was not

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JCHR (2025) 15(3), 79-87 | ISSN:2251-6727

statistically significant when compared to the healthy control group. [12] This was in accordance to various other previous studies showing lower prevalence of RAU.

When reviewing the frequency of reporting, oral lichen planus was one of the most commonly reported oral lesion in HCV individuals globally with a pooled prevalence of 11%. The global prevalence of HCV in patients with OLP is reported to be variable, with a recent meta-analysis indicating that OLP patients have a four-fold higher frequency of HCV compared to controls.[31] But it is to be noted that all the studies did not include histopathological analysis for confirmatory diagnosis of OLP. HCV replication in the oral mucosa causes a cytotoxic effect on epithelial cells and this may induce oral lichen planus. [4] The proportion of CD8+ T cells in the lamina propria appears to be higher in HCV-associated OLP compared with idiopathic OLP. CD4+ T cell clones present in the oral mucosa showed a different T-Cell Receptor-Vb chain usage than those present in the peripheral blood, suggesting a specific compartmentalization at the site of the OLP lesions. This shows that HCV-specific T cells among the lichen-infiltrating lymphocytes were not recruited as a result of the liver inflammation and may play a role in the pathogenesis of some OLP cases. [26] Also neo-antigens expressed on infected cells by HCV could lead to lichenoid inflammation. Some studies also show different genetic cytokine background of oral lichen planus patients with and without HCV infection. [28]

The cohort study conducted by **Henderson L et al** in 2001 for assessment of oral heath in HCV infected cases found that 3 out of 13 (8%) patients having dentures presented with erythematous candidiasis. Various other oral mucosal anomalies reported were frictional keratosis, hyperplastic candidosis, angular cheilitis, buccal mucosal pigmentation, petechial haemorrhages, mucosal ulcers and inflamed sublingual salivary duct openings. [23] The pooled prevalence of oral candidiasis in this study was 10%. There have been few studies on detection of oral *Candida* before, during and after IFN treatment for chronic hepatitis C. IFN therapy for HCV infection is associated with various side effects, including a greater level of fatigue, loss of appetite, weight loss, sleep problems, and depression which may lead to oral candidiasis. **Back-Brito GN et al**. demonstrated that eating disorders can lead to an increased oral *Candida* carriage. [29] As candidiasis is one of most prevalent lesions associated with systemic disorders due to its opportunistic nature and being associated with severe immunosuppression, its presence should be some kind of awareness to the possible systemic conditions for early diagnosis and treatment.

The pooled prevalence of oral leukoplakia among HCV infected individuals was 7%. **De Mattos S et al** conducted a cross-sectional survey to examine the oral mucosal conditions in chronic hepatitis C patients. The prevalence of leukoplakia was 13% in this study. Except for one case all others revealed mild epithelial dysplasia on histopathological examination. [17] In a cohort study by **Nagao et al**, leukoplakia with leukoedema was present in 1.7% of cases. 3.4% of cases presented with only leukoedema on buccal mucosa. The diagnosis of leukoplakia was made on the basis of clinical features, biopsy and subsequent histopathological examination. [21]

Gingivitis, periodontitis, angular cheilitis and pigmentation in HCV infected patients were also reported inconsistently with a varying prevalence between countries. This variation in prevalence is due to variation in sample characteristics due to diverse demographic data and also different viral genotypes involved.

The systematic review conducted on oral manifestations has certain limitations. The computed prevalence of individual oral manifestations is not an exact indication, as the clinical heterogeneity in race, habits, level of immunosuppression and gender prevalence in each study can make the comparison of studies very difficult. We have also noted that these papers originated from a limited number of countries, and often from the same group of researchers and therefore, are not necessarily widely representative. There remains obvious gap in our knowledge of HCV related oral manifestations in many developing countries in which we need to address this issue.

Conclusion

HCV infection is an important public health problem worldwide with increasing mortality rates. Patients with HCV infection can remain asymptomatic for a long time and run a subclinical course. They may

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present a number of extra hepatic manifestations, including those in the oral cavity. Patients with known chronic hepatitis who receive dental treatment are at risk for leucopenia, thrombocytopenia, and liver dysfunction, all of which can be fatal if complications of the chronic infection are not considered during treatment planning.

The presence of these lesions should warrant testing for this communicable disease. Therefore, awareness of prevalence of oral manifestations, among HCV positive patients, those caring for them and the concerned health care professionals, will facilitate early diagnosis of HCV infection and improvement in oral healthcare, thus reducing the outcome related burden of the disease.

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