Hepatitis C Virus and Lichen Planus

A Reciprocal Association Determined by a Meta-analysis

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Objective: To explore the association between hepatitis C virus (HCV) and lichen planus (LP) by performing a meta-analysis of observational studies of the association.

Data Sources: Bibliographical searches were conducted in the MEDLINE, EMBASE, and China National Knowledge Infrastructure (CNKI) databases without any language limitations.

Study Selection: Studies were selected when the following criteria were met: the coexistence of a study group and a control group, the reliable and nonselective use of the reference standards for the diagnosis of LP and HCV, and the proportion of events (the prevalence of HCV in patients with LP or the prevalence of LP in patients with HCV).

Data Extraction: Three investigators independently assessed abstracts for relevant studies, and 2 investigators independently reviewed all eligible studies.

Data Synthesis: Sixty-three articles entailing 7 studies were included in the meta-analysis. For the primary outcome of prevalence of events, the meta-analysis showed that there existed an important association between HCV and LP. In the comparison of the prevalence of HCV exposure among patients with LP with that of control participants, the odds ratio (OR) was 5.4 (95% confidence interval [CI], 3.5-8.3); in the prevalence of LP among patients with HCV compared with the prevalence among control participants, the OR was 2.5 (95% CI, 2.0-3.1). The subgroup analyses with geographical stratification did not show a significant association in studies from South Asia ($P=.21$), Africa ($P=.15$), and North America ($P=.09$), and the subgroup analyses from stratification by LP type also did not show a significant association in the isolated cutaneous type ($P=.17$). When strict criteria were applied, the results of sensitivity analysis remained robust.

Conclusion: Hepatitis C virus infection is associated with a statistically significant risk for development of LP, suggesting that the presence of either HCV or certain types of LP may be used as a predictive marker of the other in certain geographical regions.

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LICHEN PLANUS (LP) IS A chronic inflammatory benign disease that affects the skin and mucous membranes and is of squamous cell origin. It is characterized by shiny, flat-topped, pruritic, violaceous, and papulosquamous eruptions varying in size from

pin point to larger than a centimeter, mainly involving the extremities, genitalia, or oral cavity.[1] The disease shows no preference for any racial group and occurs both in men and women, mostly between the ages of 30 and 70 years, but it is uncommon in very young or elderly persons.[2] Although the first description of LP dates back to 1869,[3] its etiology has not been determined; however, it may be provoked by stress and viral infection.[4] Recently, many studies have suggested that hepatitis C virus (HCV), which affects approximately 170 million people world wide,[5] may play an important role in the pathogenesis of LP.[6] Given the controversy about the association of LP and HCV, we conducted a systematic review and meta-analysis of the existing epidemiologic studies by using a comprehensive search strategy to determine whether there is an association between LP and HCV.

METHODS

DATA SOURCES AND SEARCH STRATEGY

All relevant studies were identified using a multimethod search approach. A MEDLINE search was performed for all the studies that reported

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the association between HCV and LP by using the Medical Subject Heading terms *hepatitis C virus, hepatitis C, HCV, liver function, lichen planus, lichen LP, LP*. In addition, EMBASE, the China National Knowledge Infrastructure (CNKI), and the Web (http://scholar.google.com/schhp?hl=zh-CN) were searched for all the relevant articles. In addition, infectious disease journals were hand searched. There were no language restrictions for the search. This search strategy was performed iteratively until we did not find any new potential citations on review of the reference lists of retrieved articles.

STUDY SELECTION AND INCLUSION CRITERIA

Three of us (L.S., W.W., and Z.H.) independently screened the titles and abstracts of potentially relevant studies before retrieving the full-text articles. If a decision regarding inclusion could not be made solely on the basis of the abstract, full-text articles were retrieved and reviewed. We included case-control or control-existing studies testing the association between LP and HCV. Participants in included studies had to have a reliable diagnosis of LP and HCV infection (eg, LP had to have been diagnosed by a clinician [eg, dermatologist or dentist] or by histopathologic characteristics, and the status of HCV had to have been detected by immunological test or reverse transcriptase–polymerase chain reaction [RT-PCR]). Research groups were subjected to the nonselective use of the reference standards (ie, the reference standards for diagnosis were applied in all participants). Studies had to report the proportion of events (the prevalence of HCV in patients with LP or the prevalence of LP in patients with HCV) in the study group and the control group. In addition, strict criteria for studies also were applied: consecutive selection of participants, matching of the study group and control group, and diagnosis of HCV by RT-PCR and LP by histopathologic characteristics.

DATA EXTRACTION

Relevant data were extracted from individual studies, including author, year of publication, country, design type, characteristics of participants, prevalence of LP and HCV, and reference standard. If a study presented data obtained by using more than 1 reference standard, the results that were most consistent were selected as the gold standard. If data could not be extracted or calculated from the article with confidence, no data were entered. For non-English and non-Chinese articles, data were abstracted by a single reviewer (L.S.) with the help of translation software (the language tool in Word and the search engine available at http://translate.google.cn/). When a single study was described by more than 1 publication, we included only 1 report. We resolved disagreements about study data extraction by consensus or by discussion with a third investigator.

STATISTICAL ANALYSIS

The odds ratios (ORs) of studies were calculated as the risk estimates for associations between HCV and LP by using meta-analysis with interactive explanation.[7] For no event, a continuity correction made by adding a factor of the reciprocal of the size of the opposite arm to the cells was used[8] for studies that involved outcomes with zero cell frequencies in 1 of the 2 groups. Categorical data measures of effect were expressed as ORs presented with associated 95% CIs, and a 2-sided $P \leq .05$ was considered to be statistically significant. The heterogeneity of studies was tested by H test: when an H value was more than 1.5, or 1.2 to 1.5 plus a 95% CI not including 1.00, indicating that statistically significant heterogeneity was present among studies, we analyzed the data by using random-effects models; otherwise, we used fixed-effects models.[9] We also report the I^2 statistic as a measurement of heterogeneity that is statistically significant by defining an I^2 greater than 56% as the cutoff value.

Potential sources of heterogeneity were explored through subgroup analyses. All major features thought to contribute to between-study heterogeneity were examined a priori, including population origins (East Asia and Southeast Asia, the Middle East, South Asia, Europe, North America, South America, and Africa), study design (prospective vs retrospective and unknown), the population the control came from, sex proportion (<1 vs ≥1), the examination method of the HCV infection (immunity-based assay vs RT-PCR), and the type of LP (mucosal, cutaneous, or mucocutaneous). To identify any study that may have exerted a disproportionate influence on the summary effect, we performed sensitivity analyses to further establish the robustness of our results by applying strict inclusion criteria. To uncover possible publication bias, we assessed publication bias by using an inverted funnel plot in which the OR was plotted on a logarithmic scale on the vertical axis against the number of participants in each study on the horizontal axis (the standard error from each study).[10]

RESULTS

STUDY SELECTION

Figure 1 shows the flow of the search selection process for articles from the original sources to final acceptance for our review. The literature search identified 1865 references from the following databases: 1193 from MEDLINE, 649 from EMBASE, and 23 from CNKI. After excluding irrelevant studies by screening their titles and abstracts and eliminating uncontrolled case series, duplicate publications, and review articles by retrieving full texts, 55 articles were included. After scanning references[11-75] from selected articles, we identified an additional 8 qualified articles by hand-searching journals and searching the Web at http://scholar.google.com/schhp?hl=zh-CN. Of these 63 articles,[11-63,66-75] 7 described 2 separate studies; these separate studies are denoted as A and B in **Figure 2** and **Figure 3** and in eTables 1 and 2 (based on a table by Robinson et al[76] and available at http://www.archdermatol.com); therefore, 70 studies met the inclusion criteria and were included in the primary meta-analysis. The 70 studies identified in our review varied in characteristics (see eTables 1 and 2). Twenty-five of these studies were conducted in Europe,* 23 in East Asia and Southeast Asia,[13,37-41,44,46,56,68,70] 15 in the Middle East,† 2 in South Asia,[27,47] 5 in Africa,[11,14,50,60] 6 in North America,[25,43,45,49,67] and 5 in South America.[42,52,59,69] Fifty-eight were written in English,‡ 7 in Chinese,[37-41,56] 1 in Italian,[54] 2 in Portuguese,[42,52] and 1 in Spanish.[45] The control populations included persons seeking evaluation on surgery,[13,31,56,58] patients with dermatoses other than LP treated at a department of dermatology,§ patients with oral diseases,‖ and persons who donated

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References 16, 17, 21, 22, 26, 28-32, 36, 48, 51, 53-55, 58, 61, 63, 66, 71, 74, 75.

†*References 12, 15, 18-20, 23, 24, 33-35, 57, 62, 72, 73.*

‡*References 11-36, 43, 44, 46-51, 53, 55, 57-63, 66-75.*

§*References 14, 15, 18, 21, 22, 24-27, 29, 33, 43, 48-51, 55, 57, 59, 60, 63.*

‖*References 17, 30, 36, 37, 39, 41, 54, 59, 61, 62, 66.*

blood,¶ whereas the remainder included persons who were healthy.# Among the studies that reported age, the criterion was different, with the age for all participants ranging from 4 to 97 years. In most studies describing sex distribution, more women than men were evaluated, and the percentage of the ratio of men and women ranged from 1:4.40 to 53.5:10. The type of LP varied among studies, but oral LP (OLP) was the most common. Most studies that met our basic criteria for reference standards adopted clinical and histologic confirmation as the reference standard for LP, and used enzyme-linked immunosorbent assay (ELISA), more alternative antibody tests, or PCR as the reference standard test for HCV.

OVERALL, SUBGROUP, AND SENSITIVITY ANALYSES

Comparison of the Prevalence of HCV Exposure in Patients With LP With That in Control Participants

A statistically significant heterogeneity was detected by H test (H statistic, 2.4 [95% CI, 2.2-2.7]) and I^2 statistic (83% [95% CI, 79%-87%]), suggesting significant differences among the study results. As shown in Figure 2, the meta-analysis identified a statistically and clinically significant common OR of 5.4 (95% CI, 3.5-8.3) for the study group compared with the control group in favor of the association between LP and HCV. In subgroup analysis, much of the heterogeneity was removed within studies from East Asia and Southeast Asia, South Asia, and South America. The fixed-effect OR was statistically significant among East Asian and Southeast Asian studies (OR, 4.7 [95% CI, 3.1-7.2]) and among South American studies (OR, 6.3 [95% CI, 3.1-12.8]) but not among South Asian studies (OR, 4.0 [95% CI, 0.5-34.5]). Evidence of heterogeneity remained unchanged in Middle Eastern, European, African, and North American studies. The random-effects OR was statistically significant for Middle Eastern studies (OR, 6.4 [95% CI, 2.7-15.0]) and for European studies (OR, 4.3 [95% CI, 2.5-7.1]) but not for African studies (OR, 3.6 [95% CI, 0.6-20.3]) or for North American studies (OR, 12.3 [95% CI, 0.7-220.0]).

All control groups showed a significant association. The studies whose design type was retrospective and unknown (OR, 9.5) showed a higher risk than those whose design type was prospective (OR, 3.7), with a statistically significant difference in results for the 2 design types ($P < .05$). The studies projecting distribution of sex did not show a statistically significant difference between those with a male to female proportion of more than 1 (OR, 6.3 [95% CI, 3.7-10.5]) and those with a proportion of less than 1 (OR, 5.5 [95% CI, 3.6-8.3]). For the reference standard of HCV, a subgroup analysis showed statistical significance for immunological methods use (OR, 5.4 [95% CI, 2.9-10.1]) and PCR method (OR, 4.4 [95% CI, 3.3-5.8]).

¶References 20, 21, 35, 36, 43, 44, 46, 53, 58.
#References 12, 14, 16, 23, 28, 32, 38-40, 44, 47, 68-70, 72-75.
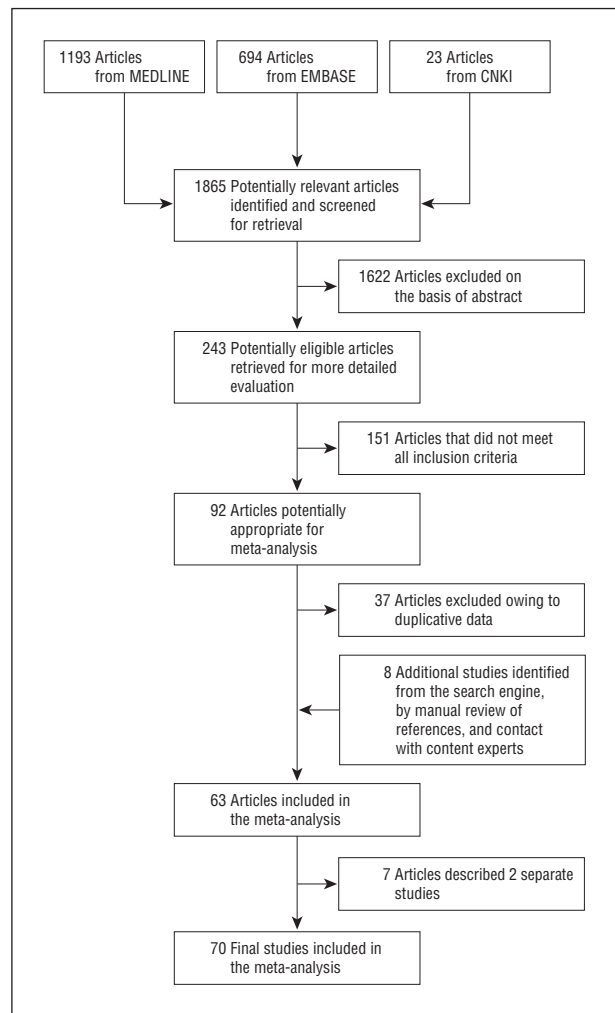
Figure 1. Flowchart of article selection. CNKI indicates the China National Knowledge Infrastructure databases.

The studies of the isolated mucosal type of LP (OR, 4.8 [95% CI, 3.0-7.7]) gave rise to a statistically significant risk effect, whereas the studies of the isolated cutaneous type provided a statistically insignificant one (OR, 10.2 [95% CI, 0.4-273.5]). Sensitivity analysis provided an effect similar to that of the original analysis when strict standards were applied. The inverted funnel plot of individual studies was symmetrical in appearance for risk of HCV infection in the study group and control group, with a similar number of studies on either side of the summary effect.

Comparison of Prevalence of LP Exposure in Patients With HCV With That in Control Participants

The heterogeneity of all 12 studies (Figure 3) was assessed using the H test, resulting in an H value of 1.1 (95% CI, 1.0-1.5) and an I^2 value of 15% (95% CI, 0%-54%), and data were pooled by the fixed-effect model. The combined OR in an overall analysis for study groups and control groups in the 12 studies was 2.5 (95% CI, 2.0-3.1), indicating an increased risk in development of LP in patients with HCV, as shown in Figure 3.

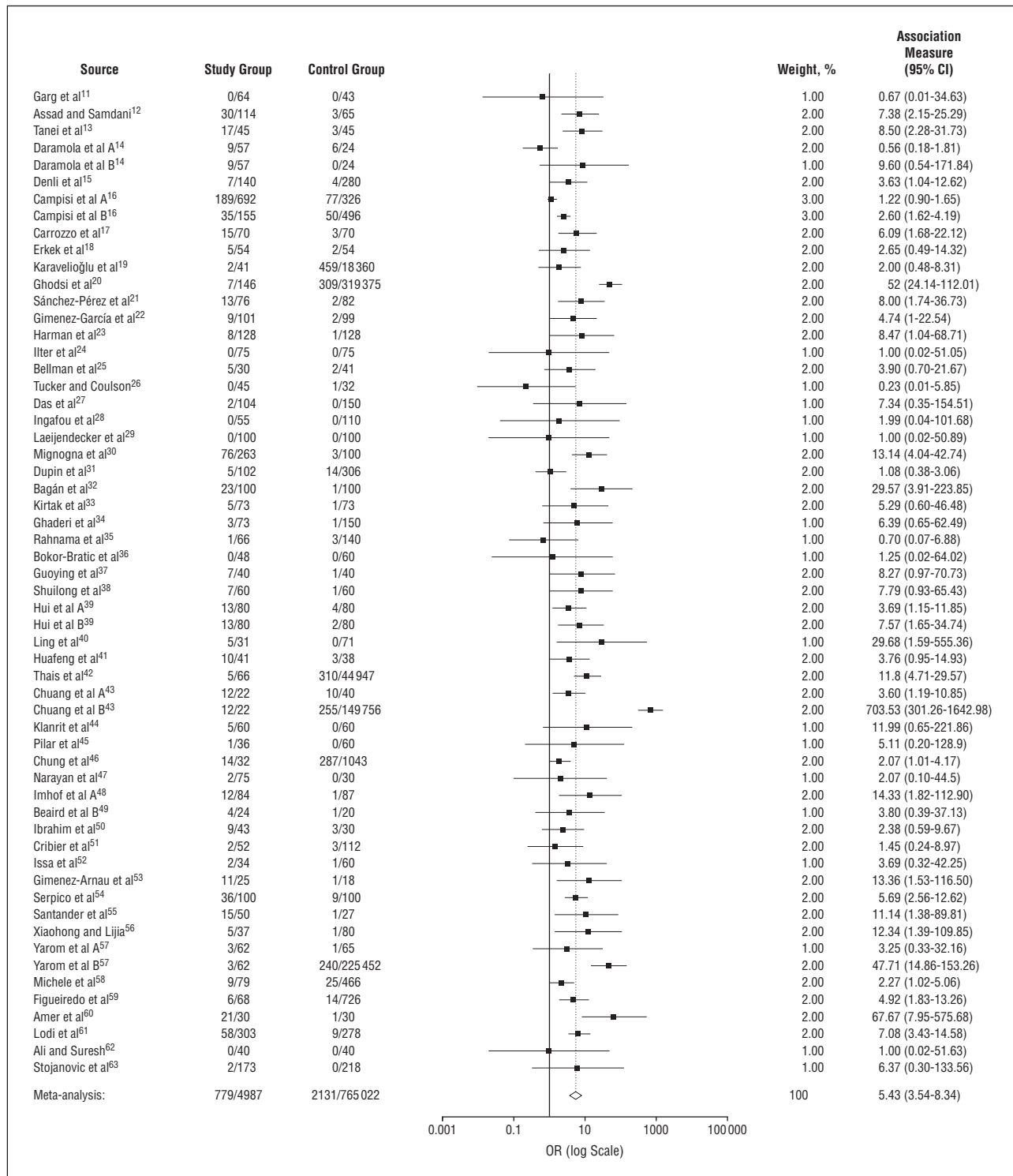| Source	Study Group	Control Group		Weight, %	Association Measure (95% CI)
Garg et al[11]	0/64	0/43		1.00	0.67 (0.01-34.63)
Assad and Samdani[12]	30/114	3/65		2.00	7.38 (2.15-25.29)
Tanei et al[13]	17/45	3/45		2.00	8.50 (2.28-31.73)
Daramola et al A[14]	9/57	6/24		2.00	0.56 (0.18-1.81)
Daramola et al B[14]	9/57	0/24		1.00	9.60 (0.54-171.84)
Denli et al[15]	7/140	4/280		2.00	3.63 (1.04-12.62)
Campisi et al A[16]	189/692	77/326		3.00	1.22 (0.90-1.65)
Campisi et al B[16]	35/155	50/496		3.00	2.60 (1.62-4.19)
Carrozzo et al[17]	15/70	3/70		2.00	6.09 (1.68-22.12)
Erkek et al[18]	5/54	2/54		2.00	2.65 (0.49-14.32)
Karavelioğlu et al[19]	2/41	459/18 360		2.00	2.00 (0.48-8.31)
Ghodsi et al[20]	7/146	309/319 375		2.00	52 (24.14-112.01)
Sánchez-Pérez et al[21]	13/76	2/82		2.00	8.00 (1.74-36.73)
Gimenez-García et al[22]	9/101	2/99		2.00	4.74 (1-22.54)
Harman et al[23]	8/128	1/128		2.00	8.47 (1.04-68.71)
Ilter et al[24]	0/75	0/75		1.00	1.00 (0.02-51.05)
Bellman et al[25]	5/30	2/41		2.00	3.90 (0.70-21.67)
Tucker and Coulson[26]	0/45	1/32		1.00	0.23 (0.01-5.85)
Das et al[27]	2/104	0/150		1.00	7.34 (0.35-154.51)
Ingafou et al[28]	0/55	0/110		1.00	1.99 (0.04-101.68)
Laeijendecker et al[29]	0/100	0/100		1.00	1.00 (0.02-50.89)
Mignogna et al[30]	76/263	3/100		2.00	13.14 (4.04-42.74)
Dupin et al[31]	5/102	14/306		2.00	1.08 (0.38-3.06)
Bagán et al[32]	23/100	1/100		2.00	29.57 (3.91-223.85)
Kirtak et al[33]	5/73	1/73		2.00	5.29 (0.60-46.48)
Ghaderi et al[34]	3/73	1/150		1.00	6.39 (0.65-62.49)
Rahnama et al[35]	1/66	3/140		1.00	0.70 (0.07-6.88)
Bokor-Bratic et al[36]	0/48	0/60		1.00	1.25 (0.02-64.02)
Guoying et al[37]	7/40	1/40		2.00	8.27 (0.97-70.73)
Shuilong et al[38]	7/60	1/60		2.00	7.79 (0.93-65.43)
Hui et al A[39]	13/80	4/80		2.00	3.69 (1.15-11.85)
Hui et al B[39]	13/80	2/80		2.00	7.57 (1.65-34.74)
Ling et al[40]	5/31	0/71		1.00	29.68 (1.59-555.36)
Huafeng et al[41]	10/41	3/38		2.00	3.76 (0.95-14.93)
Thais et al[42]	5/66	310/44 947		2.00	11.8 (4.71-29.57)
Chuang et al A[43]	12/22	10/40		2.00	3.60 (1.19-10.85)
Chuang et al B[43]	12/22	255/149 756		2.00	703.53 (301.26-1642.98)
Klanrit et al[44]	5/60	0/60		1.00	11.99 (0.65-221.86)
Pilar et al[45]	1/36	0/60		1.00	5.11 (0.20-128.9)
Chung et al[46]	14/32	287/1043		2.00	2.07 (1.01-4.17)
Narayan et al[47]	2/75	0/30		1.00	2.07 (0.10-44.5)
Imhof et al A[48]	12/84	1/87		2.00	14.33 (1.82-112.90)
Beaird et al B[49]	4/24	1/20		1.00	3.80 (0.39-37.13)
Ibrahim et al[50]	9/43	3/30		2.00	2.38 (0.59-9.67)
Cribier et al[51]	2/52	3/112		2.00	1.45 (0.24-8.97)
Issa et al[52]	2/34	1/60		1.00	3.69 (0.32-42.25)
Gimenez-Arnau et al[53]	11/25	1/18		2.00	13.36 (1.53-116.50)
Serpico et al[54]	36/100	9/100		2.00	5.69 (2.56-12.62)
Santander et al[55]	15/50	1/27		2.00	11.14 (1.38-89.81)
Xiaohong and Lijia[56]	5/37	1/80		2.00	12.34 (1.39-109.85)
Yarom et al A[57]	3/62	1/65		1.00	3.25 (0.33-32.16)
Yarom et al B[57]	3/62	240/225 452		2.00	47.71 (14.86-153.26)
Michele et al[58]	9/79	25/466		2.00	2.27 (1.02-5.06)
Figueiredo et al[59]	6/68	14/726		2.00	4.92 (1.83-13.26)
Amer et al[60]	21/30	1/30		2.00	67.67 (7.95-575.68)
Lodi et al[61]	58/303	9/278		2.00	7.08 (3.43-14.58)
Ali and Suresh[62]	0/40	0/40		1.00	1.00 (0.02-51.63)
Stojanovic et al[63]	2/173	0/218		1.00	6.37 (0.30-133.56)
Meta-analysis:	779/4987	2131/765 022		100	5.43 (3.54-8.34)

0.001　　0.1　　10　　1000　　100 000

OR (log Scale)

Figure 2. Meta-analysis of hepatitis C virus prevalence. The study group and control group are compared. In the "Study Group" and "Control Group" columns the numerators indicate the numbers of cases, and the denominators indicate the participants included. CI indicates confidence interval; OR, odds ratio. A source labeled "A" or "B" refers to 1 of the 2 studies discussed in that article.

COMMENT

Although coexistence of LP with HCV infection was first reported in 1991,[77] their association has not been proven. Given the morbidity and health care costs associated with LP, it is important to establish whether HCV has a strong association with LP. We used meta-analysis in this study to compare the carrier state of HCV in patients with a proven diagnosis of LP and latent LP in those who were HCV seropositive with that of the controls.

Our meta-analysis of 70 studies showed a statistically significant association. The OR for this association was 2.5, suggesting statistical significance when comparing LP prevalence in patients with HCV with that in
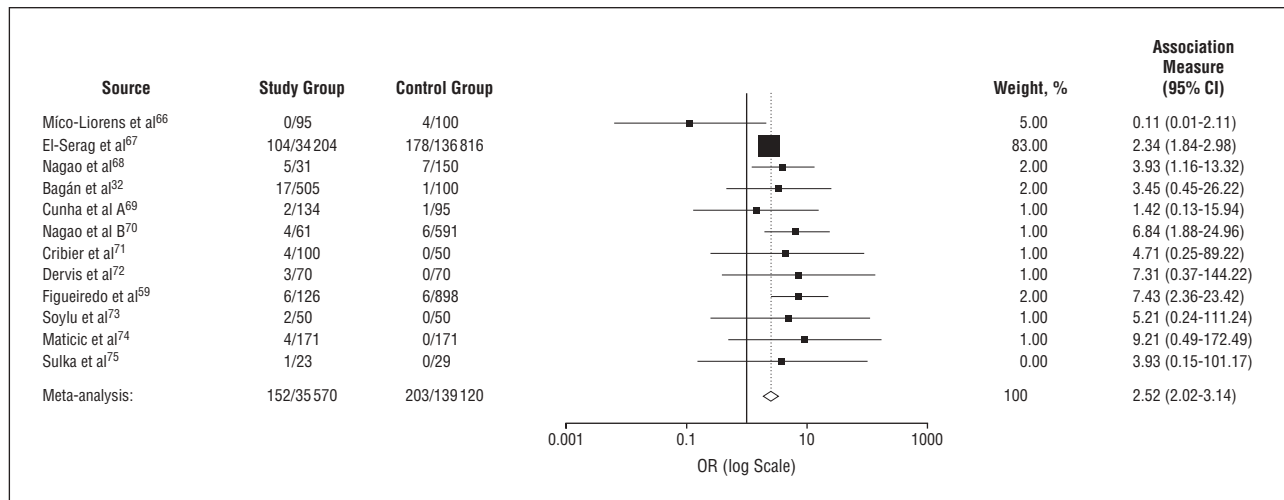
Source	Study Group	Control Group		Weight, %	Association Measure (95% CI)
Míco-Liorens et al[66]	0/95	4/100		5.00	0.11 (0.01-2.11)
El-Serag et al[67]	104/34 204	178/136 816		83.00	2.34 (1.84-2.98)
Nagao et al[68]	5/31	7/150		2.00	3.93 (1.16-13.32)
Bagán et al[32]	17/505	1/100		2.00	3.45 (0.45-26.22)
Cunha et al A[69]	2/134	1/95		1.00	1.42 (0.13-15.94)
Nagao et al B[70]	4/61	6/591		1.00	6.84 (1.88-24.96)
Cribier et al[71]	4/100	0/50		1.00	4.71 (0.25-89.22)
Dervis et al[72]	3/70	0/70		1.00	7.31 (0.37-144.22)
Figueiredo et al[59]	6/126	6/898		2.00	7.43 (2.36-23.42)
Soylu et al[73]	2/50	0/50		1.00	5.21 (0.24-111.24)
Maticic et al[74]	4/171	0/171		1.00	9.21 (0.49-172.49)
Sulka et al[75]	1/23	0/29		0.00	3.93 (0.15-101.17)
Meta-analysis:	152/35 570	203/139 120		100	2.52 (2.02-3.14)

OR (log Scale)

Figure 3. Meta-analysis of lichen planus prevalence. The study group and control group are compared. In the "Study Group" and "Control Group" columns the numerators indicate the numbers of cases, and the denominators indicate the subjects included. CI indicates confidence interval; OR, odds ratio. A source labeled "A" or "B" refers to 1 of the 2 studies discussed in that article.

controls. Both biochemical (eg, alanine aminotransferase and aspartate aminotransferase levels) and histologic parameters have been reported to be worse in infected patients than in noninfected patients, suggesting that the 2 diseases (HCV infection or LP clinic presentation) may be considered as aggravating factors for each other.

It might be argued that the true association between LP and HCV is due to heterogeneity. Although we tried to overcome this limitation by using a random-effects model to adequately capture the trade-off between the association estimates in comparisons with significant heterogeneity, which, reassuringly, were consistent with weighted estimates, the results from the meta-analysis should be accepted with caution.

We found that the association between HCV and LP was affected by the geographical sites, which was due to the varied prevalence of HCV infection. In the studies reviewed, HCV prevalence in patients with LP from Africa and North America was high and was considerably lower in South Asia. The higher prevalence of HCV infections in patients with LP was most commonly seen in Japan and Mediterranean regions.[21,78] In samples with various geographic areas, prevalence diversity of HCV contributed differentially to LP, which seemed to influence the statistical power of these studies. The peculiar differences in heterogeneity in geographic regions seen in the association of LP and HCV is difficult to explain and has been hypothesized to be the result of differences in genetic factors, such as different human leukocyte antigen types.[79,80] Also, different HCV genotypes have variable degrees of pathogenetic potential for the development of LP.[81] Socioeconomic factors may also be expressed in the geographic differences. In most studies conducted in middle- and high-income countries, the higher screening rates for HCV and identification of LP are related to advanced technology and access to health care, which lead to a stronger association between HCV and LP. Alcohol ingestion and getting tattoos, considered to be transmission routes of HCV,[82] could be involved in the development of the clinical symptoms in LP.

The choice of study and control groups is critically important for the establishment of an association between them; however, the inclusion and exclusion criteria were not described in detail in most studies. Many patients were enrolled from the dermatology department or oral medicine clinic of a university-affiliated hospital, and they are not representative of the whole population. Because patients referred to the dermatology department or clinic may be from other regions, there may be selection bias. The second limitation is the lack of sufficient clinical history. If those patients with LP who had ever been admitted to a liver clinic were more likely to be examined for HCV than those patients with LP who had never been admitted, the admitted patients with LP, with a potential risk for HCV, were more likely to be diagnosed by investigators, resulting in a higher prevalence of HCV in patients with LP. We assessed studies comparing the prevalence of HCV in those with LP in various control types separately because individual control types address different questions. Thus, the results must be interpreted cautiously, considering the advantages and limitations of each control. Those with dermatoses as a control are intended to be compared with the study group as a convenience sample. If patients with extrahepatic skin disease were entered into the dermatose control group, the association between LP and HCV would be underestimated. Thus, the healthy population and blood donors were both considered as control groups, but the 2 populations may not represent proper control groups because they had a lower seroprevalence and weak matching by age, sex, or other variables. This would result in bias toward an exaggerated difference when these populations are compared with patients with LP.

Most studies included were performed in academic institutions and used clinical symptoms and histopathologic confirmation to establish the presence or absence of LP, but potential misclassification of disease may be unavoidable. Van der Meij et al[83,84] reported that the accuracy of ascertainment of OLP by clinical and histo-

pathologic diagnoses has been found to be not very high. In fact, the clinical symptoms of some other dermatologic diseases, such as lichenoid drug reactions, are very similar to those of LP. Owing to the sparse information on the use of medicine and lichenoid drug reactions before entry into the study, the pooled results should be prudently interpreted. In studies reviewed, HCV status of participants was tested by ELISA, microparticle enzyme immunoassay, or RT-PCR, or was preliminarily tested by ELISA and further confirmed by either recombinant Western blot assay (the second generation) or RT-PCR. At present, investigators use a combination of immunological methods and nucleic acid amplification methods to improve the accuracy of results because nucleic acid amplification tests have been reported to be more sensitive than non–nucleic acid amplification tests and can test potential HCV status that non–nucleic acid amplification cannot test at the "window stage" of HCV infection.[85] However, false-positive or false-negative results sometimes cannot be avoided by nucleic acid amplification tests. Because HCV, an RNA virus belonging to the *Flaviviridae* family, may be decomposed by the RNA-degrading enzyme existing in vitro, this would prevent assays from providing a positive result, leading to decreased sensitivity. Another potential problem in the RT-PCR system is that mistakes in some steps may produce nonspecific products or no result.

Age and sex are very important potential confounding factors. In the studies reviewed, some authors reported that LP affected 0.5% to 2.0% of the population with a predilection for a mean age from the fourth to the fifth decade.[2] Only 1 study[16] stratified the study and control groups by age; therefore, we were unable to perform a subgroup analysis to dichotomize the included studies by the age. With regard to sex distribution, LP was observed more frequently in women,[86] but a significantly statistical difference between sexes was not found ($P = .07$).

Sample size bias often existed in observational studies. We had no ability to ascertain whether studies included in our review had an adequate sample size. Ghodsi et al[20] and Stojanovic et al[63] reported an a priori sample size calculation. Inadequate choice of sample size may lead to chance and exaggerate (or dilute) the association between LP and HCV. Almost all studies included in our meta-analysis are case-control studies. A shortcoming is that data from studies with retrospective design cannot establish causation because they are unable to determine whether the HCV exposure occurred before or after the onset of LP.

Even though studies have demonstrated HCV replication in LP lesions,[87] the pathogenesis of LP is not established. A concern is that HCV often coexists with human immunodeficiency virus (HIV) and the course of HCV is worse when a patient is coinfected with HIV.[88,89] Some studies showed that a functional immunosuppression owing to CD4 deficiency caused by HIV does not allow the triggering of in situ cytotoxic mechanisms leading to OLP.[90] If inclusion of HCV-positive participants with undiscovered HIV infection is different in individual groups, this would dilute any potential association between HCV and LP.

In conclusion, the results of our meta-analysis provide high-quality evidence that an important relationship exists between HCV and LP. Patients with LP may be prevented from infecting others with undetected HCV by screening patients with LP for HCV.

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Notable Notes

The Blind Man and the Paralytic Boy of Lesnovo: Diagnosis of Borderline Lepromatous Leprosy After 660 Years?

The monastery of Archangel Michael in Lesnovo, built in 1341, is located in northeastern Macedonia. Inside the monastery, the fresco of a paralytic boy guiding a blind man, which was painted in 1347, immediately draws one's attention: the spotted skin of the leprous man and the boy is in stark contrast to the divine depictions of saints and angels on the walls (**Figure**). Artistically, the figures are modeled with tranquil grace and strong facial features. The flowing and airy fabrics of the figures superimposed on the visual perspective of the background add depth to the whole scene.

Christian artists composed scenes in which lepers were immediately recognizable by red spots as early as the 9th century in the Bamberg Evangelium,[1] in the 12th century in the mosaics in the Monreale cathedral near Palermo, Italy, and in 14th century Armenian gospel iconography.[2] In agreement with the definition of leprosy from Leviticus, the artists in Lesnovo depicted a man and a boy afflicted by biblical leprosy. Biblical leprosy referred to any skin disorder characterized by ulcerating lesions. Furthermore, the artists left us an inscription above the fresco identifying the 2 main figures as the blind (man) and the paralytic (boy).[3]

Here we have 2 patients from the 14th century: a boy that cannot walk and a man that cannot see, both presenting with generalized erythematous lesions. If the 2 lepers of Lesnovo are considered as clinical cases, borderline lepromatous leprosy could be recognized. The differential diagnosis includes lepromatous leprosy, chickenpox, and measles. Chickenpox and measles rarely affect adults. Also, vision loss and the inability to walk are commonly associated with advanced types of leprosy. Full lepromatous leprosy is characterized by leonine facies and eyebrow alopecia/madarosis, which are absent in our 2 patients. Therefore, we believe that the most likely clinical diagnosis for the 2 Lesnovo patients is borderline lepromatous leprosy.

While the brilliant art of the mosaic was the artistic triumph of the Byzantine culture and accessible only to the high circles, fresco painting was adaptable, immediate, and often bold in views, and because it was less expensive, it became the property of all social strata. Easily understandable and widely accepted, fresco painting spread messages of virtue and order, giving simple answers to questions of faith, piety, and worship.

Using the "mass medium" of their time, frescography, the Lesnovo artists left us a powerful message. The 2 lepers teach us how through cooperation and teamwork we can achieve things that are otherwise out of our reach: together, the paralytic boy and the blind man could see and go where neither one could do so on his own.

Figure. The blind man and the paralytic boy of Lesnovo, a fresco in St Archangel Michael's Church, Lesnovo Monastery, Macedonia, 1347. Photograph taken on site by the authors.

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