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REVIEW ARTICLE

Hepatitis C virus infection and lichen planus: a systematic review with meta-analysis

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OBJECTIVE: Hepatitis C virus (HCV) is one of the major causes of chronic liver disease worldwide but its morbidity is also due to a variety of extra-hepatic manifestations including mixed cryoglubulinemia, non–Hodgkin lymphoma, diabetes, porphyria cutanea tarda and lichen planus. The aims of this study were to conduct a systematic review and a meta-analysis on the prevalence of HCV in lichen planus patients and on the prevalence of lichen planus in chronic HCV infection.

MATERIALS AND METHOD: Bibliographic searches were conducted in several electronic databases. Pooled data were analysed by calculating odds ratios, using a random effects model.

RESULTS AND CONCLUSIONS: Thirty-three studies comparing the seroprevalence of HCV in lichen planus patients and six reporting the prevalence of lichen planus in patients with HCV infection were included in the meta-analysis. The summary estimate showed that LP patients have significantly higher risk (odds ratio 4.85; 95% confidence interval 3.58–6.56) than controls of being HCV seropositive. A similar odds ratio of having lichen planus was found among HCV patients (4.47; 95% confidence interval 1.84–10.86). Sub-analyses indicated that variability of HCV/lichen planus association seemed only partially depending on geographic effect.

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Keywords: lichen planus; oral lichen planus; hepatitis C virus; meta-analysis

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Introduction

Hepatitis C virus (HCV) is presently considered as the main etiologic agent of both blood-borne and sporadic non-A and -B hepatitis, and is one of the major causes of chronic liver disease worldwide. However, morbidity associated with HCV infection is due not only to the sequelae of chronic liver disease, but also to a variety of extra-heaptic manifestations (EHM). According to a recent review, mixed cryoglubulinemia is the only EHM in which the association with HCV has been demonstrated by both epidemiological and pathogenetic evidences, while diseases strongly suspected to be linked to HCV include B-cell non-Hodgkin lymphoma, monoclonal gammopathies, porphyria cutanea tarda and lichen planus (LP) (Zignego *et al*, 2007).

Lichen planus is a relatively common disorder of the stratified squamous epithelia frequently involving the oral cavity exclusively (Eisen *et al*, 2005).

It is likely that LP represents a sterotype-cell mediated reaction to a variety of extrinsic antigens, altered self-antigens, or super antigens. Among the extrinsic factors, several infective agents, including some viruses and *Helicobacter pylori,* have been linked with LP but sometimes on the basis of equivocal data (Lodi *et al*, 2005; De Vries *et al*, 2006).

A possible link between hepatitis viruses and LP has been suggested by the frequent association between LP and chronic liver disease (CLD) in Mediterranean patients (Carrozzo and Gandolfo, 2003) but no pathogenic correlation could be found until HCV assays became available. The risk of chronic liver disorders in LP patients is in fact independent from alcohol consumption, and is still significantly high after adjustment for a positive hepatitis B surface antigen (HBsAg) reaction (GISED, 1990). Markers of past hepatitis B virus (HBV) infection [antibodies to hepatitis B surface antigen (HBsAb) and to hepatitis B core antigen (HBcAb)] have been reported in Spanish and Italian patients with LP (Ayala *et al*, 1986; Delolmo *et al*, 1990; Carrozzo *et al*, 1996), but with prevalence quite close the average figure in the Mediterranean area. Moreover, the recently discovered viruses, hepatitis G virus or TTV, are not associated with LP (Nagao *et al*, 1997; Lodi *et al*, 2000; Bez *et al*, 2001; Rodriguez-Inigo *et al*, 2001).

When sensitive HCV diagnostic tests became available, a great amount of case reports (Carrozzo, 2008), cohort and controlled studies suggested a link between LP and HCV infection. A systematic review investigating HCV seropositivity in LP patients was published in 2004 (Lodi *et al*, 2004) and more than 20 controlled studies were published thereafter (Bokor-Bratic, 2004; Campisi *et al*, 2004; Chung *et al*, 2004; Denli *et al*, 2004; Harman *et al*, 2004; Karavelioglu *et al*, 2004; Asaad and Samdani, 2005; Dervis and Serez, 2005; Guerreiro *et al*, 2005; Laeijendecker *et al*, 2005; Luis-Montoya *et al*, 2005; Rahnama *et al*, 2005; Das *et al*, 2006; Sulka *et al*, 2006; Ali and Suresh, 2007; Amer *et al*, 2007; de Mattos Camargo *et al*, 2007; Ghaderi and Makhmalbaf, 2007; Giuliani *et al*, 2007; Yarom *et al*, 2007). Moreover, the frequency of LP in patients with HCV infection has never been reviewed systematically.

In recent reviews devoted to HCV-EHM, conflicting statements have been made, some supporting and others discharging the link between LP and such viral infection (Sene *et al*, 2004; Ali and Zein, 2005; Palekar and Harrison, 2005; Sterling and Bralow, 2006; Galossi *et al*, 2007; Okuse *et al*, 2007; Zignego *et al*, 2007; Carrozzo, 2008) but literature was rarely reviewed with a systematic approach.

Furthermore, IFN-α and ribavirin may cause or exacerbate some muco-cutaneous disorders (Berk *et al*, 2007), including LP, sometimes leading to anti-HCV treatment withdrawal (Protzer *et al*, 1993). As a result, it is difficult to determine whether LP results from HCV, IFN-α/ribavirin, both or neither. On the other hand, there are also some concerns about the inclusion of LP patients in clinical trial of IFN-α therapy (Berk *et al*, 2007).

The aim of our study was to systematically review epidemiological data on the association between HCV infection in LP. The two null hypotheses of our study were that (ii) there is no difference between the proportion/number of anti-HCV seropositive subjects in patients affected by LP compared with control groups, against the alternative hypothesis of a difference, and (ii) there is no difference between the proportion/number of subjects affected by LP in patients HCV seropositive compared with control groups, against the alternative hypothesis of a difference.

All along the text the term LP has been used generically to indicate both skin and oral LP (OLP). When a more specific indication was opportune, the more precise terminology of skin or cutaneous LP and OLP was used.

Patients and methods

Criteria for considering studies

Studies addressing the relationship between LP and HCV seropositivity were considered. We collected either studies investigating the prevalence of HCV in LP patients or studies assessing the frequency of LP in HCV seropositive and/or infected subjects. Studies were eligible for the inclusion in the meta-analysis when they fulfilled the following criteria:

1. analytical study design as indicated by Grimes and Schulz (Grimes and Schulz, 2002), i.e. an observational study with a comparison or control group;
2. diagnosis of LP based on clinical and histological features;
3. HCV seropositivity based on serological test for circulating anti-HCV antibodies

Exclusion criteria were the following:

1. Studies involving patients with HCV and HIV co-infection
2. Studies where HCV could not be excluded from other causes of liver disease
3. Studies using references data or data from blood donors banks or historical controls
4. Duplicate studies (studies originating from the same subjects by the same investigators but published in different journals)
5. Articles providing insufficient information to calculate the OR

Search strategy for identification of studies

To identify relevant literature, bibliographical searches were performed in PubMed (January 1966 to November 2007), EMBASE (January 1988 to November 2007) CINAHL (January 1982 to November 2007) and SCOPUS (January 1960 to November 2007) databases using the following terms: 'Hepatitis C', 'Hepacivirus', 'HCV', 'lichen planus' and 'lichen*'. To identify additional studies, references lists of previously identified published papers were searched and the World Wide Web was searched by means of a search engine (http://www.google.com). The title and abstract of each article resulting from the literature search were independently reviewed by two investigators and when the article was considered relevant, the full report was obtained. Disagreements about eligibility were resolved by consensus with a third reviewer. Articles published in any language were included.

Methods of the review

Selection of studies and assessment of study quality. Every study included was assessed on the basis of: (i) characteristics of the study group (consecutive, unselected patients); (ii) appropriateness of the control group: subjects belonging to the control group must not differ importantly from those of the study group (sex and age must be matched, subjects of the control group must be selected from the study base); and (iii) prospective design (i.e. data and sera collected on purpose). Each of these criteria was rated as 'met', 'unmet' or 'unclear'. The global validity of the study was assessed using three categories: (i) low risk of bias: all criteria met; (ii) moderate risk of bias: one or two criteria unclear; and (iii) high risk of bias: at least one criterion unmet or three criteria unclear. The critical appraisal of the studies was carried out without blinding the name of the authors, institutions or journal Final decision about inclusion or exclusion was made by mutual agreement

Data about the study, its eligibility, validity, design and outcome information, were recorded on an abstraction form.

Data extraction and statistical analysis. For each study, data on the numbers of subjects of the study group and the control group with a positive outcome (HCV seropositivity among LPs, and LP among HCV seropositives), were extracted. For each study an OR and 95% CI was calculated. Where absence of events in one of the groups caused problems with computation of OR, 0·5 was added to all values for that study, except when absence of events involved both study and control groups, in which case OR was undefined (Deeks *et al*, 2001). Heterogeneity was measured calculating I^2, a statistic for quantifying inconsistency among studies. However, as heterogeneity among studies was expected on the basis of a large variability in HCV prevalence across different countries, a random effect was used to calculate the summary estimate.

Subgroup analysis was undertaken for geographical area, patients with oral lesions, age, studies excluding lichenoid reactions and researches including a confirmatory HCV test further to the screening one. Sensitivity analysis was undertaken excluding studies of lower methodological quality (i.e. studies at moderate and high risk of bias). To investigate potential for publication bias we checked for asymmetry of the funnel plot of the OR of the included studies. The statistical analysis was conducted using RevMan5, a copyrighted freeware developed by the Cochrane Collaboration, for preparing and maintaining reviews (http://www.cochrane-net.org/revman).

Results

From 447 articles identified with different search strategies, 97 potentially eligible studies were found, of them 70 studies worldwide investigated HCV seroprevalence among LP patients (Table 1) and 27 of them investigated the frequency of LP in patients with chronic HCV infection met the criteria to be included in the review (Figure 1).

HCV prevalence among LP patients

The overall prevalence of HCV in LP patients according to the 70 studies involving 6378 patients was 22.3%, with a high variability among and within countries (Table 1). Among these studies, 33 met our inclusion criteria and were considered for the systematic review (Cribier *et al*, 1994; Santander *et al*, 1994; Bellman *et al*, 1995; Gimenez-Arnau *et al*, 1995; Tanei *et al*, 1995; Carrozzo *et al*, 1996; Sanchez-Perez *et al*, 1996; Dupin *et al*, 1997; Imhof *et al*, 1997; Serpico *et al*, 1997; Bagan *et al*, 1998; Ilter *et al*, 1998; Ingafou *et al*, 1998; Mignogna *et al*, 1998; Ibrahim *et al*, 1999; Issa *et al*, 1999; Tucker and Coulson, 1999; Kirtak *et al*, 2000;

Table 1 Studies investigating HCV seroprevalence in groups of lichen planus patients

Reference	*Lichen planus patients*	*Number of HCV+ subjects*
Ali and Suresh, 2007	40	0
Amer *et al*, 2007	30	21
Asaad and Samdani, 2005	114	30
Bagan *et al*, 1994	187	28
Bagan *et al*, 1998	100	23
Beaird *et al*, 2001	24	4
Bellman *et al*, 1995	30	7
Bokor-Bratic, 2004	48	0
Campisi *et al*, 2004	859	238
Carrozzo *et al*, 1996	70	19
Chainani-Wu *et al*, 2004	31	14
Chuang *et al*, 1999	22	12
Chung *et al*, 2004	32	14
Cribier *et al*, 1994	52	2
Daramola *et al*, 2002	57	9
Das *et al*, 2006	104	2
del Olmo *et al*, 2000	169	36
de Mattos Camargo *et al*, 2007	50	1
Denli *et al*, 2004	140	7
Divano *et al*, 1992	46	11
Divano *et al*, 1994	56	13
Dupin *et al*, 1997	102	8
Dupond *et al*, 1998	28	8
Egan and Zone, 1997	29	4
Eisen, 2002	195	0
Erkek *et al*, 2001	54	7
Figueiredo *et al*, 2002	68	6
Gandolfo *et al*, 1994	105	10
Garg *et al*, 2002	64	0
Ghaderi and Makhmalbaf, 2007	73	3
Ghodsi *et al*, 2004	146	7
Gimenez-Arnau *et al*, 1995	25	11
Gimenez-Garcia and Perez-Castrillon, 2003	101	9
Giuliani *et al*, 2007	79	9
Grote *et al*, 1998	24	1
Guerreiro *et al*, 2005	66	5
Harman *et al*, 2004	128	8
Ibrahim *et al*, 1999	43	9
Ilter *et al*, 1998	75	0
Imhof *et al*, 1997	84	13
Ingafou *et al*, 1998	55	0
Issa *et al*, 1999	34	2
Karavelioglu *et al*, 2004	41	2
Khaja *et al*, 2006	21	52
Kirtak *et al*, 2000	73	5
Kirtschig *et al*, 2005	44	0
Klanrit *et al*, 2003	60	4
Laeijendecker *et al*, 2005	100	0
Lodi *et al*, 2004	303	58
Luis-Montoya *et al*, 2005	36	1
Mahboob *et al*, 2003	184	43
Mignogna *et al*, 1998	263	76
Mignogna *et al*, 2002	600	165
Nagao *et al*, 1995	45	28
Narayan *et al*, 1998	75	2
Parodi *et al*, 1996	61	13
Prabhu *et al*, 2002	65	0
Rahnama *et al*, 2005	66	1
Rebora *et al*, 1992	79	21
Rossi and Colasanto, 2000	100	13
Roy *et al*, 2000	6	0
Sanchez-Perez *et al*, 1996	78	16
Santander *et al*, 1994	50	19
Sata *et al*, 1996	45	28
Serpico *et al*, 1997	100	36
Schmitt *et al*, 1995	32	11

Table 1 (*Continued*)

Reference	*Lichen planus patients*	*Number of HCV+ subjects*
Tanei *et al*, 1995	45	17
Tucker and Coulson, 1999	45	0
van der Meij and van der Waal, 2000	55	0
Yarom *et al*, 2007	62	3
Total	6378	1420 (22.26%)

Beaird *et al*, 2001; Erkek *et al*, 2001; Daramola *et al*, 2002; Garg *et al*, 2002; Gimenez-Garcia and Perez-Castrillon, 2003; Klanrit *et al*, 2003; Bokor-Bratic, 2004; Harman *et al*, 2004; Lodi *et al*, 2004; Luis-Montoya *et al*, 2005; Rahnama *et al*, 2005; Das *et al*, 2006; Ali and Suresh, 2007; Ghaderi and Makhmalbaf, 2007; Yarom *et al*, 2007).

Characteristics of the included studies. The main characteristics of the 33 included studies are presented in Table 2. Nineteen out of 33 studies were from European countries, two from USA, two from Africa, six from Asia, two from Middle East and two from South America. Two studies were written in a language different from English: one in Portuguese and one in Italian.

Eleven included only patients with oral lesions, which were present in a variable proportion in most of the other studies. The control group was enrolled amongst dermatological patients in 12 studies, in one case some patients with potentially HCV associated dermatological conditions (porphyria cutanea tarda, cutaneous vaculitis and prurigo) were excluded, while another included psoriasis patients only. The other control groups were formed by dental patients (five studies), blood donors (four study), dental health care workers (two study), healthy subjects (two studies), patients with unrelated oral keratoses (two study), surgical patients (two studies), healthy subjects and dermatological patients (one study), HIV negative outpatients (one study); in two studies the origin of control group was not specified. The serological test adopted to detect circulating anti-HCV antibodies was a second generation ELISA in 14 studies and a third/fourth generation ELISA in 15; in four cases the characteristics of the test were not reported. Positive results were confirmed by means of another test in 14 studies (Table 2).

Critical appraisal of the included studies. On the basis of the criteria previously described, nine studies resulted at low risk of bias, 11 were judged at moderate risk of bias, and 13 at high risk of bias (Table 2). The first criterion was met in less of half the studies, since study group was clearly formed by consecutive, unselected patients with LP in only 15 of the 33 studies. Of the other two criteria, control group was adequately selected and matched in 20 cases and the study had a prospective design in 19. None of the studies published in form of letter or abstract was judged at low risk of bias.

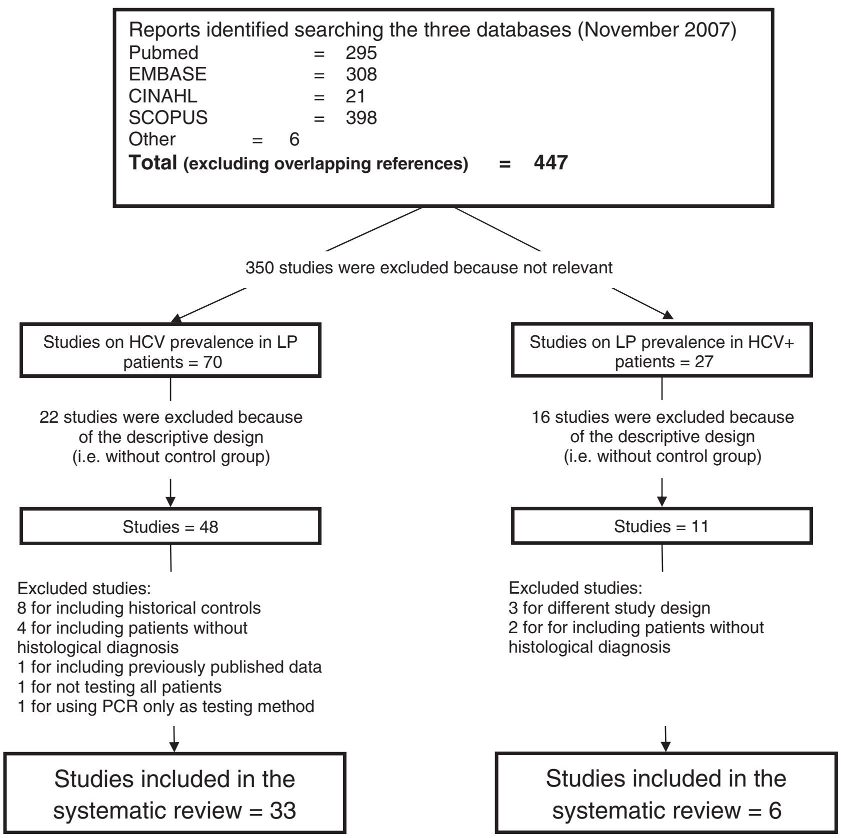

Figure 1 Flow diagram

Table 2 Characteristics of the studies included in the meta-analysis investigating HCV prevalence in lichen planus patients

		Lichen planus group		*Control group*		*Serological tests*		
Country	*Reference*	n	*Oral lesions*	n	*Provenience*	*Screening*	*Confirmatory*	*Risk of bias*
Brazil	Issa *et al*, 1999	34	9/34	60	Blood donors	ELISA 3	Unspecified	High
France	Cribier *et al*, 1994	52	4/52	112	Dermatology patients	ELISA 2	RIBA 2	Moderate
	Dupin *et al*, 1997	102	102/102	306	Surgical patients[a]	ELISA 3	RIBA 3	Moderate
Egypt	Ibrahim *et al*, 1999	43	Unspecified	30	Dermatology patients	Unspecified	Unspecified	High
Germany	Imhof *et al*, 1997	84	45/84	87	Dermatology patients	ELISA 2	RIBA 2	High
India	Das *et al*, 2006	104	Unspecified	150	HIV negative outpatients	ELISA 3	Unspecified	High
Iran	Ghaderi *et al*, 2007	73	Unclear	150	Blood donors	ELISA 3		High
	Rahnama *et al*, 2005	66	Unclear	140	Blood donors	ELISA	RIBA 2	High
Israel	Yarom *et al*, 2007	62	62/62	62	Patients with other oral conditions[b]	ELISA 3	RIBA 3	Low
Italy	Carrozzo *et al*, 1996	70	70/70	70	Patients with other oral conditions[c]	ELISA 2	RIBA 2	Low
	Serpico *et al*, 1997	100	100/100	100	Dental patients	ELISA 2	RIBA 2	Moderate
	Mignogna *et al*, 1998	263	263/263	100	Dental patients	ELISA 2	RIBA 2	High
	Lodi *et al*, 2004	303	303/303	278	Dental patients	ELISA 3	Line immunoassy	Low
Japan	Tanei *et al*, 1995	45	37/45	45	Surgical patients (orthopedic)	ELISA 2	Unspecified	Moderate
Mexico	Luis-Montoya *et al*, 2005	36	Unclear	60	Blood donors	ELISA 3	Unspecified	High
Nepal	Garg *et al*, 2002	86	29/86	43	Unknown	ELISA 3	–[e]	Moderate
Nigeria	Daramola *et al*, 2002	57	Unspecified	48	Healthy and dermatology patients	ELISA 2	Unspecified	Moderate
Saudi Arabia	Alì *et al*, 2007	40	40/40	40	Dental patients	ELISA 3	Unspecified	Moderate
Serbia	Bokor-Bratic *et al*, 2004	48	48/48	60	Dental patients	ELISA 4	Unspecified	Low
Spain	Santander *et al*, 1994	50	Unspecified	27	Dermatology patients	ELISA 2	PCR	High
	Gimenez-Arnau *et al*, 1995	25	Unspecified	18	Unknown	Unspecified	Unspecified	High
	Sanchez Perez *et al*, 1996	78	56/78	82	Dermatology patients	ELISA 2	Unspecified	Low
	Bagan *et al*, 1998	100	100/100	100	Healthy subjects	ELISA 2	RIBA 2 or 3	Moderate
	Gimenez-Garcia *et al*, 2003	101	53/101	99	Dermatology patients	ELISA 2	RIBA 2	Low
Thailand	Klanrit *et al*, 2003	60	60/60	60	Dental health care workers	ELISA 3	RNA	High
Turkey	Ilter *et al*, 1998	75	Unspecified	75	Dermatology patients	Unspecified	–[e]	Moderate
	Kirtak *et al*, 2000	73	27/73	73	Dermatology patients[d]	ELISA 3	Unspecified	Moderate
	Erkek *et al*, 2001	52	7/52	54	Dermatology patients	ELISA 3	Unspecified	Low
	Harman *et al*, 2004	128	52/128	128	Healthy subjects	ELISA 3	Unspecified	Low
UK	Ingafou *et al*, 1998	55	55/55	110	Dental health care workers	ELISA 3	–[e]	High
	Tucker *et al*, 1999	45	13/45	32	Dermatology patients	ELISA 2	RIBA 3	Low
USA	Bellman *et al*, 1995	30	Unspecified	41	Dermatology patients	ELISA 2	RIBA 2	Moderate
	Beaird *et al*, 2001	24	Unspecified	20	Dermatology patients (psoriasis)	Unspecified	Unspecified	High

[a]Excluding patients with hepatic diseases, receiving haemodialysis and transplant patients.
[b]Hyperkeratosis, oral candidiasis, recurrent aphthous stomatitis, pemphigus vulgaris, mucous membrane pemphigoid, benign oral growth.
[c]Leukoplakia, frictional keratosis, verrucous carcinoma, nicotinic stomatitis, white spongious nevus.
[d]Excluding patients with porphyria cutanea tarda, cutaneous vaculitis and prurigo.
[e]All subjects were negative.

Meta-analysis. The total number of patients of the included studies was 5404. In five studies no seropositive patients were found in either group. In these studies OR could not be calculated. The proportion of HCV-positive subjects was higher in the lichen planus group compared with controls in all the other studies but two, the OR of HCV seropositivity in patients with LP varying between 0.23 (95% CI: 0.01–5.85) and 15.94 (95% CI: 2.00–127.22). The summary estimate OR for all studies was 4.85 (95% CI: 3.58–6.56) (Figure 2), showing a statistically significant difference in the proportion of HCV seropositive subjects among lichen planus patients, compared with controls. Interestingly, despite the high geographical variety, heterogeneity of the results was not significant (I^2 = 10.7%).

Subgroup analysis. In 11 studies all patients included had oral lesions (with and without cutaneous lesions), also in this subgroup, HCV seroprevalence was significantly more common among LP patients than controls (OR = 5.56 95% CI: 3.50–8.81). The summary estimate OR increased considerably in the Mediterranean studies (OR = 6.99 95% CI: 4.92–9.94), while, in the studies from Northern Europe, halved, becoming not significant (OR = 2.14 95% CI: 0.59–7.69). The sum-

Study or subgroup	Lichen planus Events	Lichen planus Total	Controls Events	Controls Total	Weight	Odds ratio M-H, Random, 95% CI
Ali 2007	0	40	0	40		Not estimable
Garg 2002	0	64	0	43		Not estimable
Ilter 1998	0	75	0	75		Not estimable
Ingafou 1998	0	55	0	110		Not estimable
Bokor Bratic 2004	0	48	0	60		Not estimable
Tucker 1999	0	45	1	32	0.9%	0.23 [0.01, 5.85]
Rahnama 2005	1	66	3	140	1.7%	0.70 [0.07, 6.88]
Daramola 2002	9	57	6	48	6.1%	1.31 [0.43, 3.99]
Cribier 1994	2	52	3	112	2.6%	1.45 [0.24, 8.97]
Dupin 1997	8	102	14	306	8.5%	1.78 [0.72, 4.36]
Ibrahim 1999	9	43	3	30	4.1%	2.38 [0.59, 9.67]
Yarom 2007	3	62	1	62	1.7%	3.10 [0.31, 30.67]
Issa 1999	2	34	1	60	1.5%	3.69 [0.32, 42.25]
Beaird 2001	4	24	1	20	1.7%	3.80 [0.39, 37.13]
Erkek 2001	7	54	2	54	3.2%	3.87 [0.77, 19.57]
Gimenenz Garcia 2003	9	101	2	99	3.4%	4.74 [1.00, 22.54]
Luis Montoya 2005	1	36	0	60	0.9%	5.11 [0.20, 128.90]
Kirtak 2000	5	73	1	73	1.8%	5.29 [0.60, 46.48]
Bagan 1998	23	100	5	100	7.1%	5.68 [2.06, 15.62]
Serpico 1997	36	100	9	100	10.2%	5.69 [2.56, 12.62]
Bellman 1995	7	30	2	41	3.1%	5.93 [1.14, 31.02]
Ghaderi 2007	3	73	1	150	1.7%	6.39 [0.65, 62.49]
Lodi 2004	58	303	9	278	11.7%	7.08 [3.43, 14.58]
Das 2006	2	104	0	150	1.0%	7.34 [0.35, 154.51]
Carrozzo 1996	19	70	3	70	4.9%	8.32 [2.33, 29.66]
Harman 2004	8	128	1	128	2.0%	8.47 [1.04, 68.71]
Tanei 1995	17	45	3	45	4.6%	8.50 [2.28, 31.73]
Klanrit 2003	4	60	0	60	1.0%	9.64 [0.51, 183.05]
Sanchezperez 1996	16	78	2	82	3.6%	10.32 [2.29, 46.58]
Mignogna 1998	76	263	3	100	5.5%	13.14 [4.04, 42.74]
Gimenez Arnau 1995	11	25	1	18	1.8%	13.36 [1.53, 116.50]
Imhof 1997	13	84	1	87	2.0%	15.75 [2.01, 123.31]
Santander 1994	19	50	1	27	2.0%	15.94 [2.00, 127.22]
Total (95% CI)		**2544**		**2860**	**100.0%**	**4.85 [3.58, 6.56]**
Total events	372		79			

Heterogeneity: Tau^2 = 0.07; Chi^2 = 30.23, df = 27 (P = 0.30); I^2 = 11%
Test for overall effect: Z = 10.24 (P < 0.00001)

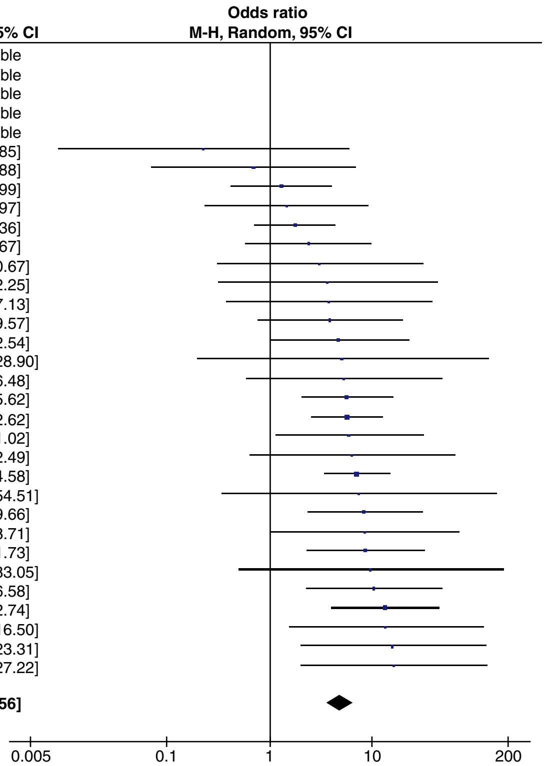

Figure 2 Forest plot of odds ratio of HCV seropositivity (and 95% confidence intervals) in patients with lichen planus

mary estimate OR of studies from US was similar to the global one (OR = 5.09; 95% CI: 1.33–19.41) whereas the corresponding figure for Africa was even lower than in Northern Europe (OR = 1.65; 95% CI: 0.69–3.95). The pooling data of studies with a LP group with a mean age of 50 years or less showed that even in LP groups of younger age, the frequency of HCV seropositivity was significatively higher than in control groups (OR = 3.43 95% CI: 2.02–5.85).

Only 12 of the studies included in the meta-analysis clearly ruled out the possibility of a drug-induced lichenoid reaction but the OR still indicated a significant higher risk of HCV seropositivity in LP than in controls (3.91; 95% CI: 2.17–7.04) (Figure 3). Similarly, when we considered studies i including a confirmatory HCV test further to the screening one, the OR was close to the global one (4.76; 95% CI: 3.07–7.41).

Sensitivity test and publication bias. When studies with high and moderate risk of bias were excluded from all the meta-analysis the summary estimate did not change significantly (Figure 4). The visual examination of the symmetry of the funnel plot did not suggest large publication bias (Figure 5).

LP prevalence among HCV patients
From the articles resulting from the different search strategies, 27 potentially eligible studies were identified, 16 were excluded because they had no control group (descriptive design), three for the different study design and clinical diagnosis and two for lack of histological diagnosis (Figure 1).

Characteristics of the included studies. The main characteristics of the 6 included studies are presented in Table 3. Two studies were from Brazil, and one each from France, Poland, Spain and Turkey. The control group was enrolled among dental patients in 3 studies, in two cases among healthy subjects and in one case among HCV-, HBV- and HIV- liver disease patients. In all studies HCV status was detected by ELISA and then confirmed by PCR or RIBA.

Critical appraisal of the included studies. On the basis of the criteria previously described, two studies resulted at low risk of bias, two were judged at moderate risk of bias, and two at high risk of bias. Only two studies clearly stated that the study group was formed by consecutive patients (Table 3).

Meta-analysis. The total number of patients of the included studies was 2197. In all six studies the prevalence of LP was higher among HCV-positive subjects compared with controls, the OR varying between 1.42 (95% CI: 0.13–15.94) and 7.43 (95% CI: 2.36–23.42). The summary estimate OR for all studies was 4.47 (95% CI: 1.84–10.86) (Figure 6), showing a statistically significant difference in the proportion of LP prevalence among HCV-positive subjects, compared with controls. As for the previous analysis, despite high geographical variety, heterogeneity of the results was not significant (I^2 = 0%).

Only three out of six studies (Bagan *et al*, 1998; Figueiredo *et al*, 2002; Cunha *et al*, 2005) reported detailed data on anti-HCV treatments. In 2 studies

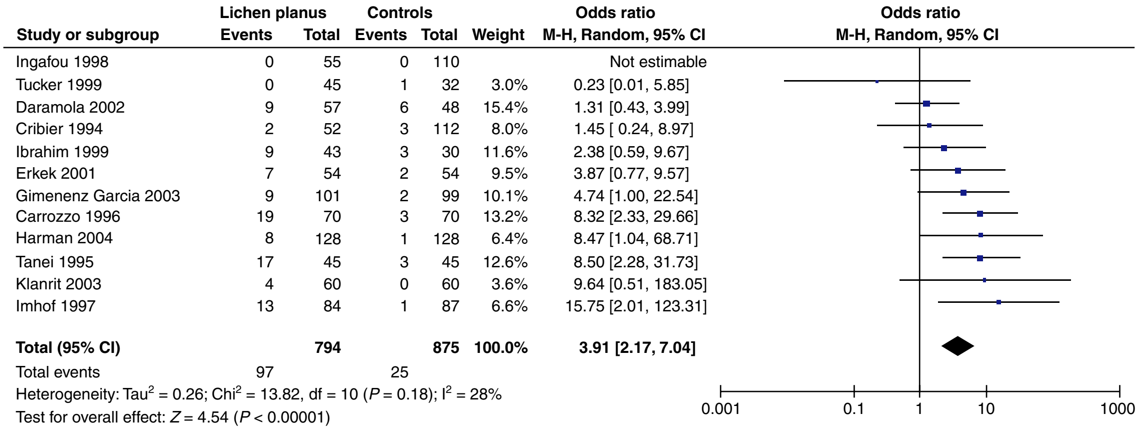

Figure 3 Subanalysis: forest plot of odds ratio of HCV seropositivity (and 95% confidence intervals) in patients with lichen planus, in studies that ruled out the possibility of drug-induced lichenoid reactions

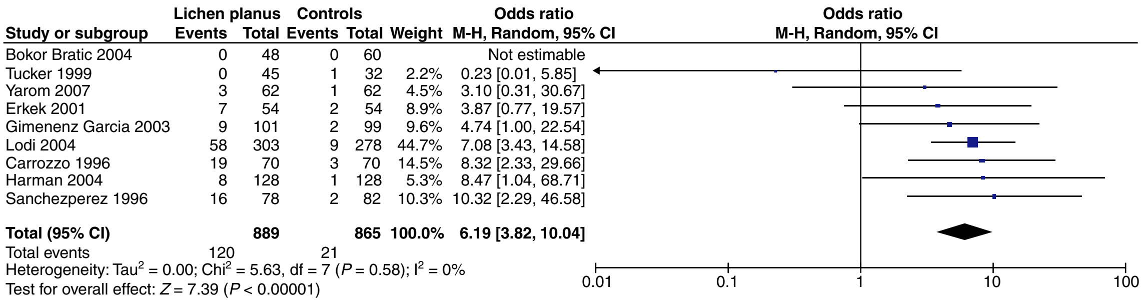

Figure 4 Sensitivity test: forest plot of odds ratio of HCV seropositivity (and 95% confidence intervals) in studies at low risk of bias

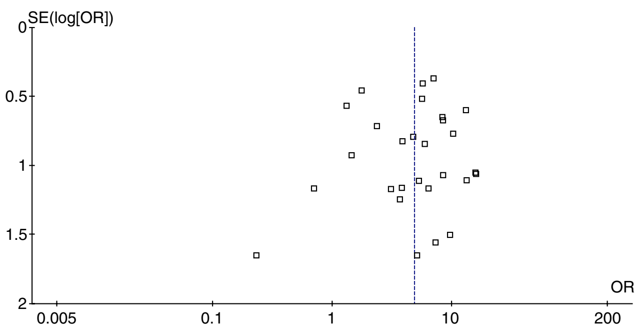

Figure 5 Funnel plot of the studies included in the review investigating HCV prevalence in lichen planus patients

(Figueiredo *et al*, 2002; Cunha *et al*, 2005), 37.5% of the patients with LP were previously exposed to IFN-α whereas the third study (Bagan *et al*, 1998) specifically stated that no significant differences were observed in the incidence of OLP between those patients who received interferon and those who did not.

Subgroup analysis. LP frequency was significantly higher among HCV-positive patients than controls either in Europe (OR = 4.26 95% CI: 1.13–16.10) or in Brazil (OR = 4.73 95% CI: 1.55–14.42).

Sensitivity test. When studies with high and moderate risk of bias were excluded from the meta-analysis the summary estimate was still statistically significant (OR = 6.97 95% CI: 2.16–22.52).

The visual examination of the symmetry of the funnel plot did not suggest large publication bias.

Discussion

In this systematic review we firmly confirm the association between HCV infection and LP. According to the meta-analysis, the summary estimate of OR showed that LP patients have about a five fold higher risk than the controls of being HCV seropositive and the OR for exclusive OLP was not substantially different from the global one. Moreover, quite the same OR was found analysing the prevalence of LP among patients with CLD due to HCV infection. However, the data showed a marked study and geographical variability, with the relationship between HCV and LP being prevalent in Japan, Mediterranean countries and the USA. This figure explains the strong regional connotation of the association among LP and HCV infection that was observed mainly in Southern Europe where HCV is highly prevalent. Interestingly, a similar geographic variability has been demonstrated for other EHM linked to HCV infection, such as porphyria cutanea tarda, lymphoma and even mixed cryoglobulinemia (Gisbert *et al*, 2003; Dal and Franceschi, 2006; Cohen Tervaert *et al*, 2007).

Several factors could be potentially responsible for the observed variability in results. These may include misclassification of LP, the highly variable prevalence of HCV infection across the world, differences in the viral characteristics of HCV, differences in genetic

Table 3 Characteristics of the studies included in the meta-analysis investigating lichen planus prevalence in HCV positive patients

		HCV subjects				*Controls*		
				Serological tests				
Country	*Reference*	n	*Characteristics*	*Screening*	*Confirmatory*	n	*Provenience*	*Risk of bias*
Brazil	Figueiredo *et al*, 2002	126	Consecutive patients with HCV diagnosis	ELISA 2	RNA	898	Dental patients	Low
	Cunha *et al*, 2005	134	Patients with other viral hepatitis were excluded	ELISA 3	RNA	95	Dental patients	Moderate
France	Cribier *et al*, 1998	81	HIV and HBV DNA excluded	ELISA 3	RNA	50	HCV-, HBV- and HIV- liver disease patients	Low
Poland	Sulka *et al*, 2006	39	23 chronic hepatitis and 16 chirrosis	ELISA[a]	RIBA[a]	29	Dental patients	High
Spain	Bagan *et al*, 1998	505	From Hepatology Unit	ELISA[a]	RIBA[a]	100	Healthy controls	High
Turkey	Dervis and Serez, 2005	70	Co-existent liver disease and treatment with antiviral or immunomodulatory agents were excluded	ELISA[a]	RNA[a]	70	Healthy controls	Moderate

[a]Not otherwise specified.

susceptibility to HCV-induced LP, variability in the studies design and biases.

To avoid misclassification of LP, we decided to include in the meta-analysis only studies in which the clinical diagnosis of LP was confirmed histologically. Some studies have shown variability in both interobserver and intraobserver reliability in the clinicopathological assessment mainly of OLP (van der Meij and van der Waal I, 2003). However, a histological confirmation of the clinical diagnosis is worldwide accepted as a gold-standard practice in both LP and OLP studies.

Several medications including IFN-α and ribavirin can trigger mucocutaneous lichenoid reactions (McCartan and McCreary, 1997; Berk *et al*, 2007). However, IFN-α has been reported to have also no influence (Pawlotsky *et al*, 1995b) or even to ameliorate LP (Doutre *et al*, 1992; Strumia *et al*, 1993; Hildebrand *et al*, 1995; Pedersen, 1998)both clinically and histologically (Nagao *et al*, 1999). If lichenoid drug reactions are misdiagnosed and included in the samples of those with LP, it would result in an overestimation of the association between LP and HCV. Only a minority of the studies included in the meta-analysis stated clearly that a diagnosis of lichenoid reaction was excluded but when they were analysed together a significant increased risk of being HCV-seropositive in LP patients was still found. Regarding specifically the anti-HCV treatment, while in some HCV-infected patients the lichenoid lesions could be secondary to anti-HCV therapy (Giuliani *et al*, 2007), it is unlikely that in the majority of the published studies most of the patients were exposed to antiviral treatments. Significantly, in the largest published study on EHM in HCV-infected patients (not included in the meta-analysis because the clinical diagnosis was not histologically confirmed in all the patients) showing a significant association between LP and HCV infection (El-Serag *et al*, 2002), less than 5% of 32.204 studied patients received antiviral therapies. In an another study (Bagan *et al*, 1998), no significant differences in the frequency of OLP were observed between patients who received interferon-alpha (IFN-α) and those who did not.

Even if this meta-analysis highlighted a significant difference between Northern and Southern Europe, the pooled data from African studies with the highest HCV prevalence in the general population did not show a significant association (Ibrahim *et al*, 1999; Daramola *et al*, 2002). This suggests that any LP-HCV association

Study or subgroup	HCV positive subject Events	HCV positive subject Total	Controls Events	Controls Total	Weight	Odds ratio M-H, Fixed, 95% CI
Cunha 2005	2	134	1	95	19.9%	1.42 [0.13, 15.94]
Sulka 2006	1	39	0	29	9.5%	2.30 [0.09, 58.48]
Bagan 1998	17	505	1	100	27.9%	3.45 [0.45, 26.22]
Cribier 1998	4	81	0	50	10.1%	5.86 [0.31, 111.28]
Dervis 2005	3	70	0	70	8.2%	7.31 [0.37, 144.22]
Figueiredo 2002	6	126	6	898	24.3%	7.43 [2.36, 23.42]
Total (95% CI)		**955**		**1242**	**100.0%**	**4.47 [1.84, 10.86]**
Total events	33		8			

Heterogeneity: Chi² = 1.98, df = 5 (P = 0.85); I² = 0%
Test for overall effect: Z = 3.30 (P = 0.0010)

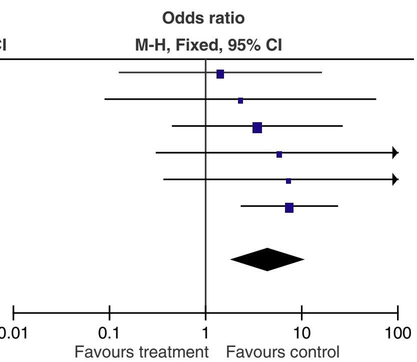

Figure 6 Forest plot of odds ratio of lichen planus prevalence (and 95% confidence intervals) in HCV seropositive patients

cannot be only explained on the basis of HCV endemicity. Indeed, the studies investigating the frequency of LP among HCV-positive subjects showed prevalences generally higher than expected, independently of the geographical origin.

Viral factors (such as genotype or viral load) seem to be ruled out by the observation that LP can be associated world-wide with the same genotypes commonly found in patients without LP (Pawlotsky *et al*, 1995a; Lodi *et al*, 1997), though mainly genotype 1b seems associated with LP, and it could be uncommon in the UK (Harris *et al*, 1999).

Genetic differences among different populations should be also taken into account. HCV-related OLP appears associated mainly with the HLA-DR6 allele in Italy (Carrozzo *et al*, 2001) whereas it does not in UK (Carrozzo *et al*, 2005). However, a comparison study of the OLP-positive/HCV-positive group with an OLP-negative/HCV-positive group is necessary to ultimately test this plausible hypothesis.

Some controversial data could have being caused by the small cohort size in a number of studies. Indeed, the majority of the studies included less than 100 subjects. As a result some studies, mainly coming from countries with low prevalence of HCV infection (Ilter *et al*, 1998; Ingafou *et al*, 1998; Garg *et al*, 2002; Bokor-Bratic, 2004; Laeijendecker *et al*, 2005; Ali and Suresh, 2007) showed the lack of any case or control positive to HCV serology. In those cases, the key question is whether the power of such studies was sufficient to detect any difference in the prevalence of HCV. For example, in one of the above studies, performed in Netherlands (Laeijendecker *et al*, 2005), 100 patients with OLP and 100 controls were recruited. Considering a prevalence of HCV infection in Netherlands of 0.5% (Van der Poel *et al*, 1991) and estimated risk of three (in this meta-analysis the odd ratio of being HCV infected in lichen planus patients from Northern Europe was 2.14), the power of such a study is only 20% (with an alpha error of 0.05, two tales). To obtain an acceptable power of 80%, more than 400 patients and 400 controls should have been recruited.

Age is a possible confounder because, in many populations, the prevalence of HCV exposure varies in different age groups (Alter, 2007), and older individuals have a higher prevalence of LP. However, the meta-analysis seems to confute the hypothesis that the high frequency of HCV seropositivity found in LP groups is caused by the increased prevalence of HCV infection in elderly patients (Campisi *et al*, 2004). Indeed, the subgroup analysis of studies with LP patients ≤50 years still showed a significant association with HCV infection.

Given the design of most of the case-control and cohort studies published, it is impossible to establish whether the HCV exposure occurred before or after the onset of LP. As a result, HCV-infected patients might have an increased risk of developing LP or conversely, patients with LP could have an enhanced risk of HCV infection. A very recent epidemiologic study from Japan suggests that OLP prevalence in HCV-infected patients increased significantly as the subjects grew older (Nagao *et al*, 2007) suggesting that the patients are very likely first infected with HCV and only later develop LP. This prospective study suggests also that the duration of the infection should be a potential source of heterogeneity in the published studies. Moreover, in countries where the prevalence among the LP-free subjects is low, the spread of the virus might be recent and not yet produced full consequences on LP development. Thus, in countries with a very low prevalence of HCV, LP should be probably better identified in HCV-infected patients rather than seeking to find HCV infection in LP patients (Carrozzo, 2001). Notably, in this meta-analysis we could not include any study looking for LP in chronic HCV infected from countries with low HCV prevalence. It has to be considered, however, that such a study could possibly require the recruitment of a large number of patients for being significant making it very difficult on a practical base and possibly clinically negligible.

Clinical implications of the results presented in this systematic review are particularly relevant. A high proportion of patients affected by HCV-associated chronic hepatitis may have persistently normal aminotransferase levels and recent data suggest that only a minority of people with HCV in Europe are aware of their infection (Merkinaite *et al*, 2008), thus testing for HCV patients with LP can lead to the diagnosis of a condition for which treatments are available and precautions can be useful to avoid further spread. Moreover, because chronic HCV infection can lead to cirrhosis and hepatocellular carcinoma (Eisen *et al*, 2005; Alter, 2007) and OLP is a potentially malignant disorder, an early diagnosis and a proper management might save lives and being beneficial in reducing health care costs.

In conclusion, this systematic review and meta-analysis shows that LP may be significantly associated with HCV infection mainly in Mediterranean countries, in Japan and USA. All the sub-analyses and the sensitivity assessments done strongly and consistently suggest this possible association. Because the HCV can replicate in the skin and in the oral mucosa and HCV-specific T cells have been found in OLP specimen (Carrozzo *et al*, 2002; Pilli *et al*, 2002), the virus could be involved in the pathogenesis of at least some OLP cases, probably via an immunological pathway still to be defined.

Finally, some of the controversial epidemiological data published could have been influenced by methodological biases (such as misclassification of the disease, small sample size, and recent acquisition of HCV, etc.) further to a generic geographic effect linked to world-wide HCV prevalence.

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