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Clinical and Laboratory Investigations

Lichen planus and hepatitis C virus: a multicentre study of patients with oral lesions and a systematic review

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Summary

Background An association between hepatitis C virus (HCV) infection and lichen planus (LP) has been investigated, but results have been inconsistent.

Objectives To investigate the relationship between LP and HCV seropositivity.

Methods In a cross-sectional study we tested the sera of 303 consecutive newly diagnosed patients with histologically proven LP referred to three Italian centres for the presence of anti-HCV IgG. A comparable control group was also tested. Next, in a systematic review, studies were identified by searching different databases in April 2004. Inclusion criteria were: (i) analytical study design; (ii) clinical and histological diagnosis of LP; and (iii) serological test for anti-HCV antibodies as main outcome. The risk of bias was assessed on the basis of characteristics of the study group, appropriateness of the control group and study design. Pooled data were analysed by calculating odds ratios (ORs), using a random effects model.

Results In the cross-sectional study, nearly one in five (19·1%) of the LP group was HCV positive, while a much lower prevalence of infection was found in the control group (3·2%) [OR 7·08; 95% confidence interval (CI) 3·43–14·58]. The systematic review yielded 25 relevant studies, six of which had a low risk of bias. There was a statistically significant difference in the proportion of HCV-seropositive subjects among patients with LP, compared with controls (OR 4·80; 95% CI 3·25–7·09). Following subgroup analyses, the variability of HCV prevalence in patients with LP seemed to depend on geographical area, but not on age.

Conclusions Anti-HCV circulating antibodies are more common in patients with LP than in controls, although such an association may not be significant in some geographical areas.

Key words: hepacivirus, hepatitis C virus infection, lichen planus, systematic review

Lichen planus (LP) is a mucocutaneous disease of chronic inflammatory nature, commonly seen in dermatological and dental clinics. Although many aspects of the pathogenesis of LP have recently been clarified,[1] no aetiological agent has been identified so far. LP has been described in association with numerous systemic conditions, including immunologically mediated diseases, infections and malignancies, but the evidence has been equivocal.[2] In the last 15 years an increasingly strong association between LP and chronic hepatic disease has been suggested.[3] Since the first report of a patient with LP who was infected with hepatitis C virus (HCV),[4] an RNA virus identified in 1989[5] and currently considered a leading cause of chronic liver disease, the link between LP and this virus has been the subject of numerous reports investigating the prevalence of HCV infection in groups of patients with LP. Unfortunately, the results of such reports are not consistent, varying from 0[6] to > 60%.[7]

We aimed: (i) to investigate the prevalence of HCV seropositivity in a large group of patients with oral LP

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in three Italian cities, and to compare it with a specially selected control group; and (ii) to analyse the currently available evidence to test the null hypothesis that there is no difference between the proportion/number of HCV-seropositive subjects in patients with LP compared with control groups.

Subjects and methods

Cross-sectional study

This multicentre cross-sectional study included data from three Italian cities, two from the north (Milan and Brescia) and one from the centre of the country (Rome). The case groups were formed by consecutive patients with a clinical and histological diagnosis of oral LP, attending the Oral Medicine clinics of three university dental schools. Control groups comprised patients without known hepatic diseases, attending the clinics of the three dental schools for reasons other than oral mucosal diseases. The sera of all the subjects were tested for the presence of anti-HCV IgG by means of a third-generation enzyme-linked immunosorbent assay (ELISA) (Vitros ECi Immunodiagnostic System; Ortho-Clinical Diagnostics, Raritan, NJ, U.S.A.), according to the manufacturer's instructions. Positive results were confirmed by a line immunoassay (Inno-Lia HCV Ab III Update). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each group and for the total of the subjects enrolled in the three cities.

Systematic review

Studies addressing the relationship between LP and HCV seropositivity were included in the present systematic review when they fulfilled the following criteria: (i) analytical study design as indicated by Grimes and Schulz,[8] i.e. an observational study with a comparison or control group; (ii) clinical and histological diagnosis of LP; and (iii) serological test for circulating anti-HCV antibodies as main outcome. To identify relevant literature, we searched MEDLINE, EMBASE and LILACS databases in April 2004 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 examined and when the article was considered relevant, the full report was obtained.

Every study included was assessed by one reviewer (G.L.) on the basis of: (i) characteristics of the study group (consecutive, unselected patients with LP); (ii) appropriateness of the control group: subjects belonging to the control group must not differ importantly from those of the study group, apart from the diagnosis of LP (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. Data about the study, its eligibility, validity, design and outcome information, were recorded on an abstraction form.

For each study, data were extracted on the numbers of patients with LP and controls who were anti-HCV positive, and on the total numbers of patients and controls. For each study an OR and 95% CI was calculated. Where absence of events (seropositive patients) 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.[9] 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, and origin of the control group. Sensitivity analysis was undertaken (i) excluding studies of lower methodological quality (i.e. studies at high risk of bias) and (ii) excluding data from the present multicentre study. 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 Rev Man Analyses 1, the statistical package of Review Manager 4.2, a copyrighted freeware developed by the Cochrane Collaboration, for preparing and maintaining reviews (http://www.cochrane-net.org/revman).

Results

Cross-sectional study

At the end of the study the case group was formed by 303 patients (211 women, 92 men; mean age 61·2 years, range 28–88) with a clinical and histological diagnosis of oral LP; 85 patients had an atrophic or erosive variant of the oral disease, while the remaining 218 patients had a reticular or plaque form. Skin lesions compatible with cutaneous LP were detected in just 11 patients. The control group comprised 278 subjects (159 women, 119 men; mean age 61·4 years, range 33–85). Fifty-eight subjects (19·1%) of the case group were HCV seropositive in a third-generation anti-HCV ELISA test compared with nine of the control group (3·2%). The difference between the prevalence of HCV seropositivity in the two groups was statistically significant (OR 7·08; 95% CI 3·43–14·58). The results for the three centres are shown in Table 1.

Systematic review

Characteristics of the studies. From 416 articles identified by the different search strategies, 42 potentially eligible studies were identified (Fig. 1). Of these, 16 were excluded because they had no control group (descriptive design), one was excluded for including patients without histological diagnosis[10] and one was excluded[11] for reporting data published in a previous article.[12] Results of the current cross-sectional study were also included. The main characteristics of the 25 studies included are presented in Table 2.[12–35] Seventeen of the 25 studies were from European countries, two from the U.S.A., two from Africa, three from Asia and one from South America. Two studies were written in a language other than English: one in Portuguese[13] and one in Italian.[19]

Eight studies included only patients with oral lesions, which were present in a variable proportion in most of the other studies. The control group was enrolled among dermatological patients in 13 studies: in one case some patients with potentially HCV-associated dermatological conditions (porphyria cutanea tarda, cutaneous vasculitis and prurigo) were excluded,[30] while another included psoriasis patients only.[35] The other control groups comprised dental patients (three studies), surgical patients (two studies), healthy subjects (two studies), dental healthcare workers (two studies), blood donors (one study) and patients with unrelated oral keratoses (one study); in two studies the origin of the control group was not specified. One study included two control groups.[12] The serological test adopted to detect circulating anti-HCV antibodies was a second-generation ELISA in 13 studies and a

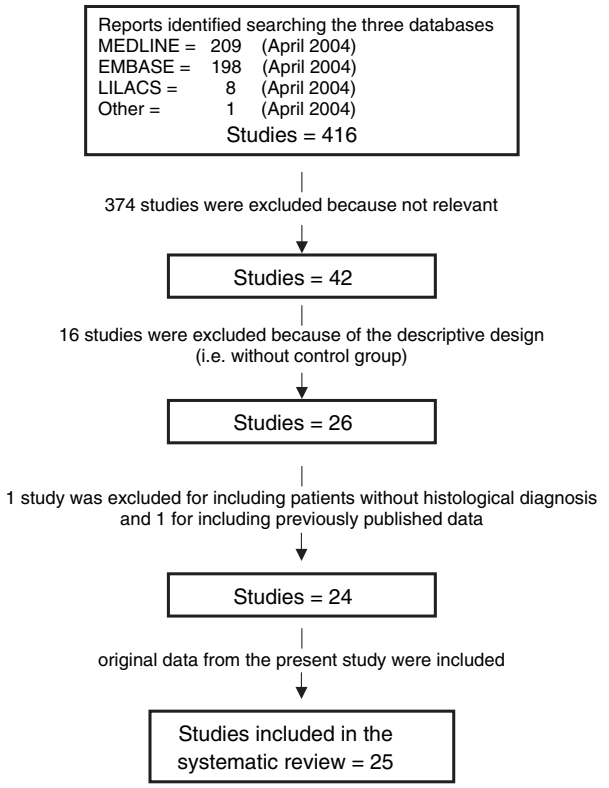

Figure 1. Flow diagram.

Table 1. Characteristics and hepatitis C virus (HCV) prevalence in three groups of Italian patients

	Lichen planus group			Control group			
	Sex ratio (F/M)	Mean age; range (years)	HCV prevalence	Sex ratio (F/M)	Mean age; range (years)	HCV prevalence	OR (95% CI)
Milan	98/46	61·7; 28–88	30/144 (20·8%)	58/38	62·4; 33–82	4/96 (4·2%)	6·05 (2·05–17·80)
Brescia	58/19	59·8; 28–79	19/77 (24·7%)	46/54	61·2; 32–75	3/100 (3·0%)	10·59 (3·00–37·35)
Rome	55/27	61·8; 34–87	9/82 (11·0%)	55/27	60·4; 39–85	2/82 (2·4%)	4·93 (1·03–23·58)
Total	211/92	61·2; 28–88	58/303 (19·1%)	159/119	61·4; 32–85	9/278 (3·2%)	7·08 (3·43–14·58)

OR, odds ratio; CI, confidence interval.

Table 2. Characteristics of the included studies

		Lichen planus group		Control group		Serological tests	
Country	Reference (first author and year)	*n*	Patients with oral lesions	*n*	Provenance	Screening	Confirmatory
Brazil	Issa 1999[13]	34	9/34	60	Blood donors	ELISA 3	Unspecified
France	Cribier 1994[14]	52	4/52	112	Dermatology patients	ELISA 2	RIBA 2
	Dupin 1997[15]	102	102/102	306	Surgical patients[a]	ELISA 3	RIBA 3
Egypt	Ibrahim 1999[16]	43	Unspecified	30	Dermatology patients	Unspecified	Unspecified
Germany	Imhof 1997[17]	84	45/84	87	Dermatology patients	ELISA 2	RIBA 2
Italy	Carrozzo 1996[18]	70	70/70	70	Patients with unrelated oral keratoses[b]	ELISA 2	RIBA 2
	Serpico 1997[19]	100	100/100	100	Dental patients	ELISA 2	RIBA 2
	Mignogna 1998[20]	263	263/263	100	Dental patients	ELISA 2	RIBA 2
	Lodi 2004 (present data)	303	303/303	278	Dental patients	ELISA 3	Line immunoassay
Japan	Tanei 1995[21]	45	37/45	45	Surgical patients (orthopaedic)	ELISA 2	Unspecified
Nepal	Garg 2002[22]	86	29/86	43	Unknown	ELISA 3	–[d]
Nigeria	Daramola 2002a[12]	57	Unspecified	24	Healthy subjects	ELISA 2	Unspecified
	Daramola 2002b[12]	57	Unspecified	24	Dermatology patients	ELISA 2	Unspecified
Spain	Santander 1994[23]	50	Unspecified	27	Dermatology patients	ELISA 2	PCR
	Gimenez-Arnau 1995[24]	25	Unspecified	18	Unknown	Unspecified	Unspecified
	Sanchez-Perez 1996[25]	78	56/78	82	Dermatology patients	ELISA 2	Unspecified
	Bagan 1998[26]	100	100/100	100	Healthy subjects	ELISA 2	RIBA 2 or 3
	Gimenez-Garcia 2003[27]	101	53/101	99	Dermatology patients	ELISA 2	RIBA 2
Thailand	Klanrit 2003[28]	60	60/60	60	Dental healthcare workers	ELISA 3	RNA
Turkey	Ilter 1998[29]	75	Unspecified	75	Dermatology patients	Unspecified	–[d]
	Kirtak 2000[30]	73	27/73	73	Dermatology patients[c]	ELISA 3	Unspecified
	Erkek 2001[31]	52	7/52	54	Dermatology patients	ELISA 3	Unspecified
U.K.	Ingafou 1998[32]	55	55/55	110	Dental healthcare workers	ELISA 3	–[d]
	Tucker 1999[33]	45	13/45	32	Dermatology patients	ELISA 2	RIBA 3
U.S.A.	Bellman 1995[34]	30	Unspecified	41	Dermatology patients	ELISA 2	RIBA 2
	Beaird 2001[35]	24	Unspecified	20	Dermatology patients (psoriasis)	Unspecified	Unspecified

ELISA, enzyme-linked immunosorbent assay; RIBA, recombinant immunoblot assay (2, second generation; 3, third generation); PCR, polymerase chain reaction. [a]Excluding patients with hepatic diseases, receiving haemodialysis and transplant patients. [b]Leucoplakia, frictional keratosis, verrucous carcinoma, nicotinic stomatitis, white sponge naevus. [c]Excluding patients with porphyria cutanea tarda, cutaneous vasculitis and prurigo. [d]All subjects were negative.

third-generation ELISA in eight; in four cases the characteristics of the test were not reported. Positive results were confirmed by means of another test in 13 studies.

Critical appraisal of the included studies. On the basis of the criteria previously described, six studies were judged to be at low risk of bias, 10 at moderate risk, and nine at high risk of bias (Table 3). The first criterion was met in about one third of the studies, as the study group was clearly formed by consecutive, unselected patients with LP in only 10 of the 25 studies. Of the other two criteria, the control group was adequately selected and matched in 15 cases and the study had a prospective design in 14. None of the studies published in the form of letter or abstract was judged to be at low risk of bias.

Data analysis. The total number of subjects in the included studies was 4057. One of the studies was considered twice in the meta-analysis because the authors included two control groups, with different characteristics, giving opposing results when compared with the study group.[12] This solution was judged to be better (more conservative) than the possible alternatives (to combine the two control groups or to choose just one of them). In three studies no seropositive patients were found in either group.[22,29,32] In these studies the OR could not be calculated. The proportion of HCV-positive subjects was higher in the LP group compared with controls in all but two of the other studies, the OR for HCV seropositivity in patients with LP varying between 0·23 (95% CI 0·01–5·85)[33] and 15·94 (95% CI 2·00–127·22).[23]

The summary estimate OR for all studies was 4·80 (95% CI 3·25–7·09) (Fig. 2), showing a statistically significant difference in the proportion of HCV-seropositive subjects among patients with LP, compared with controls. As would be expected, the heterogeneity test showed statistically significant heterogeneity ($P = 0·04$).

Table 3. Methodological quality of the included studies

Reference (first author and year)	Criteria			Risk of bias
	Study group	Control group	Study design	
Carrozzo 1996[18]	Met	Met	Met	Low
Erkek 2001[31]	Met	Met	Met	Low
Gimenez-Garcia 2003[27]	Met	Met	Met	Low
Lodi 2004	Met	Met	Met	Low
Sanchez-Perez 1996[25]	Met	Met	Met	Low
Tucker 1999[33]	Met	Met	Met	Low
Bagan 1998[26]	Unclear	Met	Unclear	Moderate
Bellman 1995[34b]	Unclear	Met	Unclear	Moderate
Cribier 1994[14]	Met	Unclear	Met	Moderate
Daramola 2002[12]	Unclear	Met	Met	Moderate
Dupin 1997[15]	Unclear	Met	Met	Moderate
Garg 2002[22]	Met	Unclear	Met	Moderate
Ilter 1998[29b]	Unclear	Met	Met	Moderate
Kirtak 2000[30]	Unclear	Met	Unclear	Moderate
Serpico 1997[19]	Unclear	Met	Unclear	Moderate
Tanei 1995[21]	Unclear	Met	Met	Moderate
Beaird 2001[35b]	Unmet	Unclear	Unmet	High
Gimenez-Arnau 1995[24a]	Unclear	Unclear	Unclear	High
Ibrahim 1999[16]	Met	Unmet	Met	High
Imhof 1997[17]	Met	Met	Unmet	High
Ingafou 1998[32]	Unclear	Unmet	Unclear	High
Issa 1999[13]	Unclear	Unmet	Unclear	High
Klanrit 2003[28]	Unclear	Unmet	Met	High
Mignogna 1998[20]	Unclear	Unclear	Unclear	High
Santander 1994[23a]	Unclear	Unclear	Unclear	High

[a]Abstract. [b]Letter.

Subgroup analysis. As illustrated in Figure 3, eight studies included only patients with oral LP (with and without cutaneous lesions). The summary estimate OR for these studies (5·71; 95% CI 3·48–9·37) was not substantially different from the global one. When the studies from two geographical areas (Northern Europe and Mediterranean basin) were analysed separately, the heterogeneity test showed a good homogeneity in the two subgroups ($P = 0{\cdot}11$ and $P = 0{\cdot}88$, respectively). The summary estimate OR increased considerably in the Mediterranean studies (6·63; 95% CI 4·68–9·40), but halved in the studies from Northern Europe, becoming nonsignificant (2·14; 95% CI 0·59–7·69). The pooled data from studies with a study group with a mean age of ≤ 50 years showed that even in LP groups of younger age, the frequency of HCV seropositivity was significantly higher than in control groups (OR 3·62; 95% CI 1·73–7·60). When characteristics of the control groups were considered, the association of LP and HCV seropositivity was confirmed for studies enrolling controls among dermatological patients (OR 4·72; 95% CI 2·76–8·05) or dental and surgical patients (OR 5·95; 95% CI 3·39–10·44). In studies with healthy subjects or blood donors as controls, the OR, although higher than 1, was not significant (OR 2·16; 95% CI 0·39–11·88).

Sensitivity test. As shown in Figure 4, when studies with high risk of bias were excluded from the meta-analysis the summary estimate OR did not change substantially (4·08; 95% CI 2·54–6·55). All the analyses were also repeated excluding the data from the present study, without producing significant changes in the summary estimates (data not shown). Visual examination of the symmetry of the funnel plot did not suggest a large publication bias.

Discussion

HCV infection is a global health problem: 170 million persons may be infected worldwide,[36] and the proportion of HCV-positive individuals varies from < 1% in Northern European countries to > 15% in Egypt.[37] The prevalence data for the countries represented in the studies included in the systematic review are summarized in Table 4.

One of the prominent aspects of HCV infection is the frequent presence of putative extrahepatic manifestations. For some of these, namely mixed cryoglobulinaemia[38] and membranoproliferative glomerulonephritis,[39] the association with HCV infection is now well established, while for others it is still under debate. This is the case for LP, a relatively common condition whose association with chronic hepatic disease was described years before identification of HCV.[3]

The present cross-sectional study and systematic review seem to confirm the association between LP and the presence of circulating anti-HCV antibodies. This does not strictly equate with HCV infection, although the high rate of chronicity of the infection (75%) would suggest that most seropositive patients are also infected, as shown by the few studies where serum RNA was used as a confirmatory test.[17,18,23,25,28,31,34]

The results of this multicentre cross-sectional study, the largest of its kind, demonstrate that HCV immunoglobulins are a common finding in the sera of Italian patients with LP, independent of the geographical area. HCV seroprevalence in the three study groups ranged between 11% and 24·7%. This variability is possibly due to chance or to differences in group size, or may be due to differences in seroprevalence in the study population, although in this case larger differences among control group prevalences would be expected.

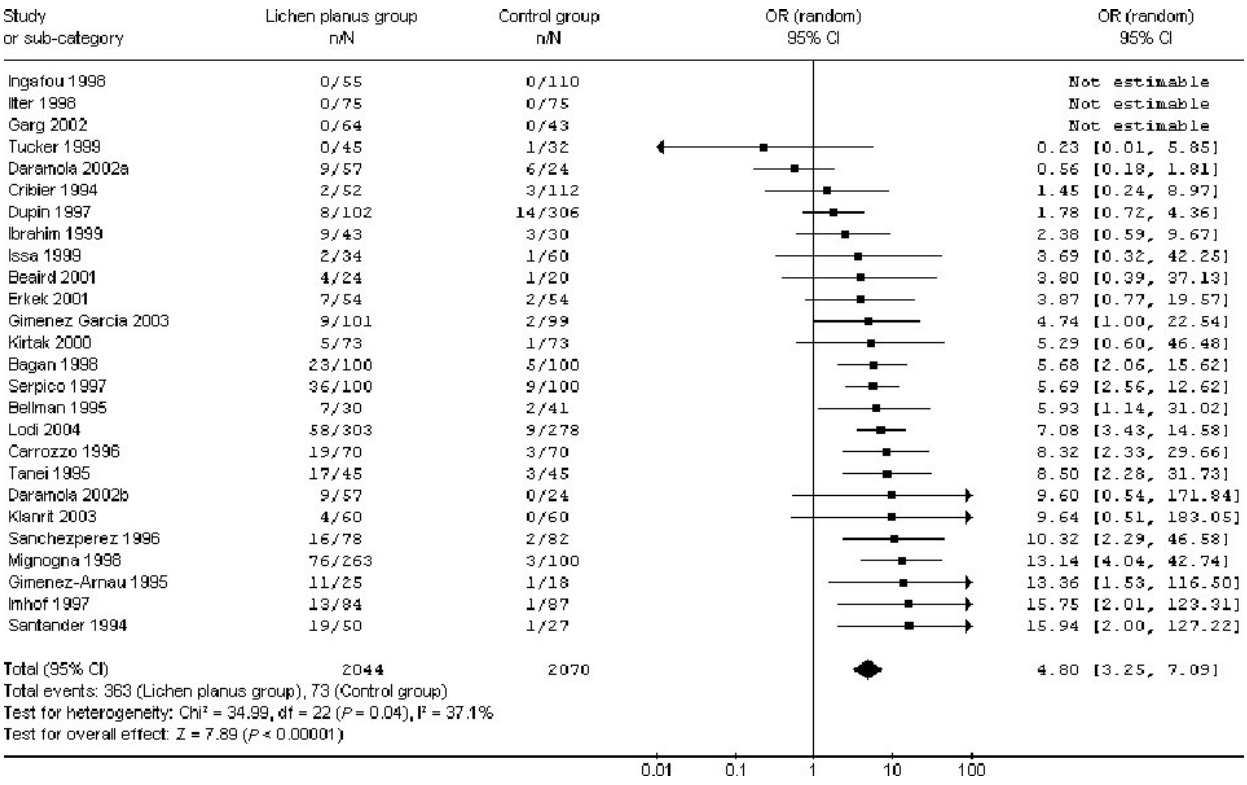

Figure 2. Forest plot of odds ratio (OR) of hepatitis C virus seropositivity [and 95% confidence interval (CI)] in patients with lichen planus.

The results of the present cross-sectional study are consistent with those of the previous controlled studies included in the systematic review. In all but two of these studies the proportion of HCV-seropositive subjects was higher among patients with LP than among controls, and this difference was statistically significant in 11 of 26 comparisons (one study had two comparisons). The summary estimate OR for all included studies was 4·80 (95% CI 3·25–7·09), indicating a higher risk for patients with LP to be HCV seropositive, compared with subjects without LP, in other words indicating an association between the two conditions.

The heterogeneity found among the studies was expected because of the highly variable prevalence of HCV infection across the world. For this reason a random effect model was adopted. The variability of HCV infection prevalence as source of heterogeneity was in part confirmed when subgroup analysis by geographical area was undertaken, resulting in a marked reduction of heterogeneity.

The overall quality of the included studies was relatively satisfactory: only nine of 25 studies were judged at high risk of bias. The composition of the study group was the most critical criterion, being met in only 10 of 25 studies. It must be emphasized that critical appraisal of observational studies is particularly difficult because of the many potential sources of errors and bias that are virtually impossible to control and assess fully.

Publication bias is considered another central issue in systematic reviews of observational studies.[40] For this reason, our search strategy included not only the usual biomedical databases but also non-English sources and the world wide web, where we found useful studies not included elsewhere. In addition, visual examination of the funnel plot did not suggest gross publication bias.

The association between HCV infection and LP has been questioned. A high prevalence of HCV infection in the general population, especially in subjects aged > 50 years, has been indicated as a possible confounding factor in studies investigating the relationship between HCV and LP. The hypothesis is that, as most patients with LP are aged > 50 years, the high frequency of HCV seropositivity found in LP groups is just the normal prevalence for the corresponding age group. The results of the present review seem to confute such a hypothesis. In 16 of the 25 included studies, the control group was sex- and age-matched

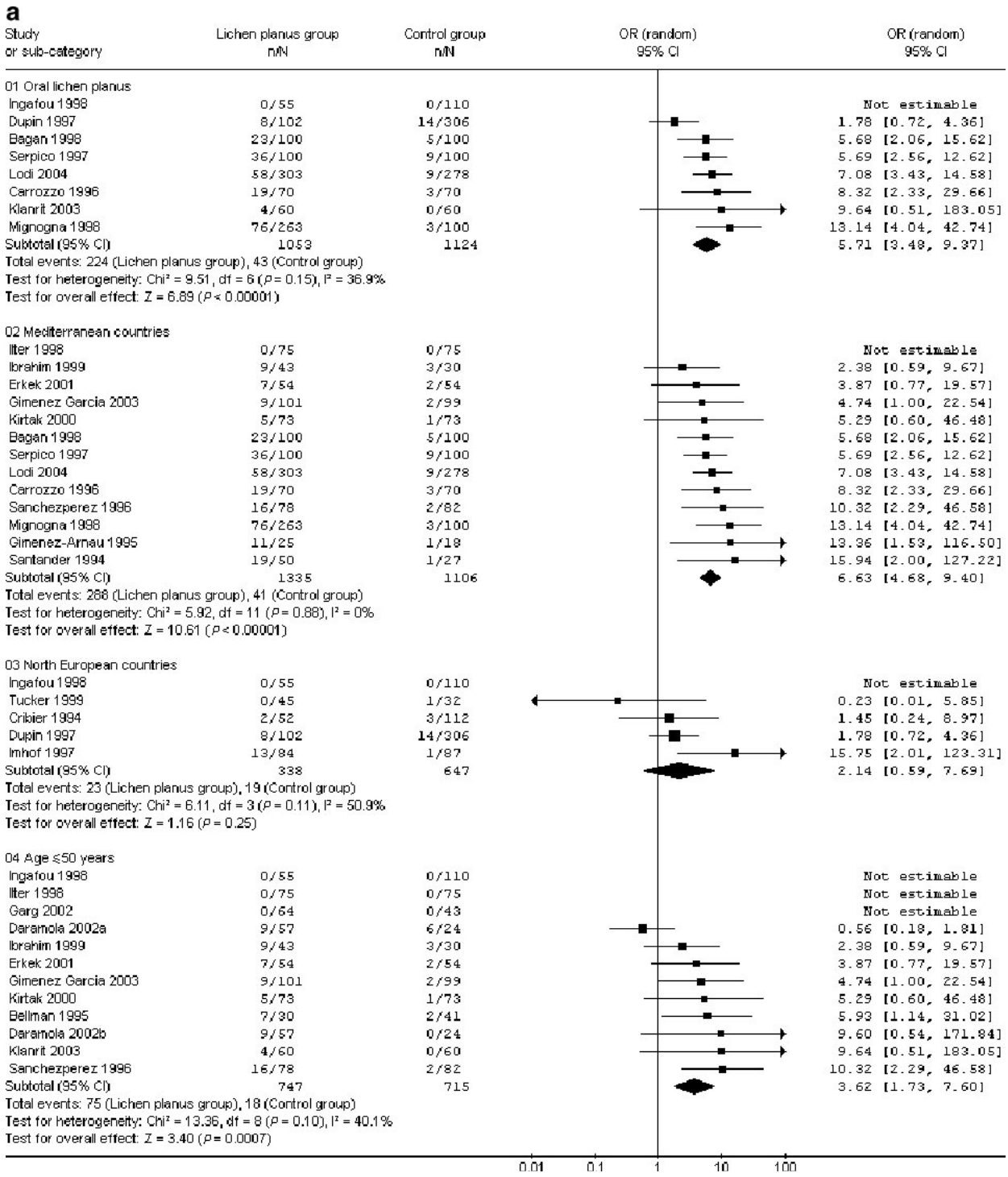

Figure 3. Subgroup analysis. (a) Patients with oral lesions, geographical area and patients aged ≤ 50 years. (b) Control group selection. OR, odds ratio; CI, confidence interval.

with the study group and thus the difference in HCV seroprevalence between the two cannot be ascribed to age of the patients with LP. In addition, the subgroup analysis of studies with LP patients ≤ 50 years also showed an association between HCV infection and LP in these cases. Furthermore, the studies from the countries with the highest HCV prevalence in the general population (Egypt and Thailand) showed a

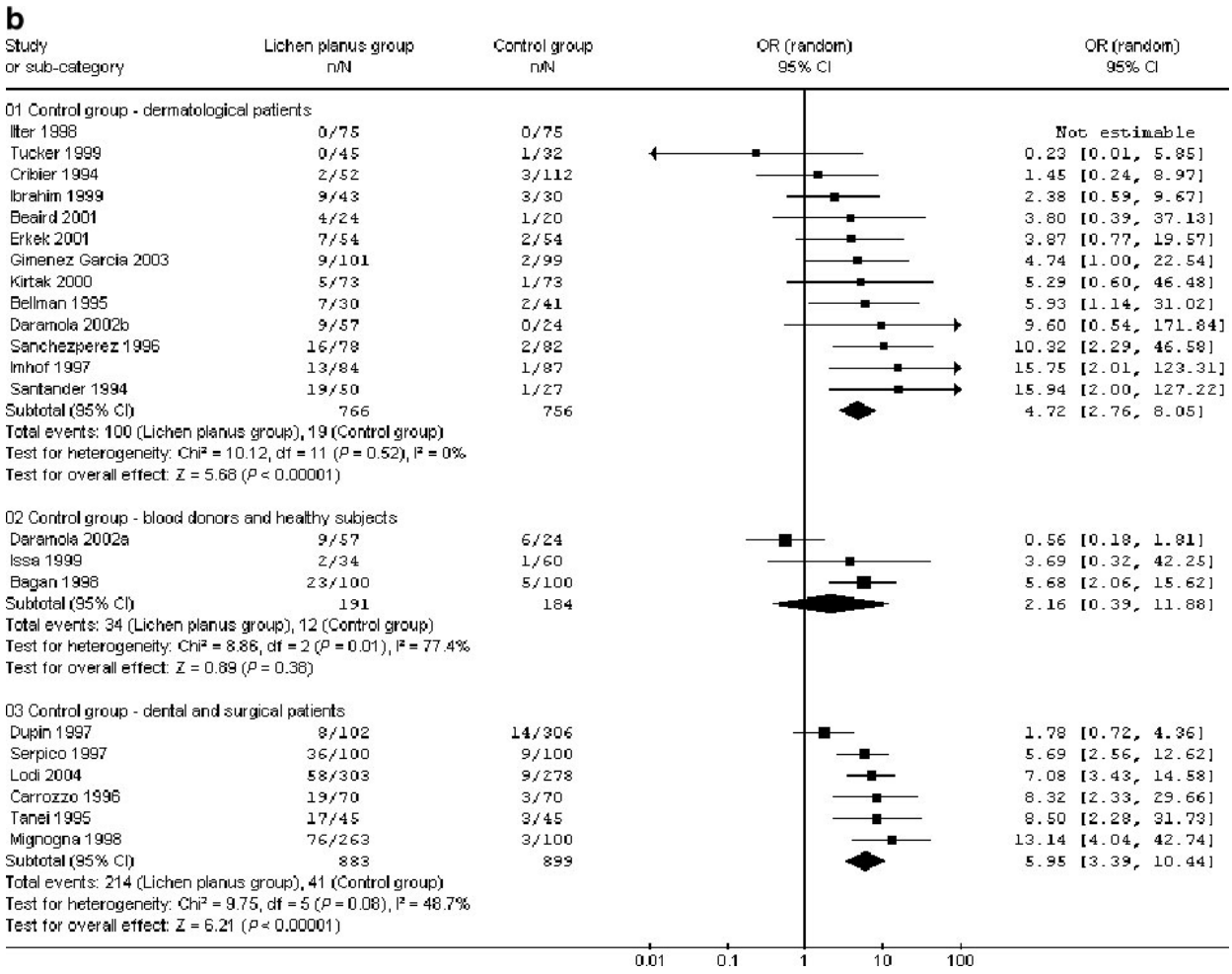

Figure 3. Continued.

negative or nonsignificant association, showing that high prevalence in the general population and in specific age groups cannot completely explain the LP–HCV association.

Controlled studies investigating LP frequency in HCV-infected patients are few and with relatively small study groups:[26,41,42] they reported a prevalence of LP of about 4%, although estimates from uncontrolled studies range from about 1%[43] to 20%.[44] A recent case–control study showed a significant twofold increase in LP prevalence among 34 204 HCV-positive subjects compared with 136 816 controls.[45] Notably, the members of the study group were significantly younger than those in the control group (45·2 vs. 56·9 years).

Although an association between LP and HCV seems to be confirmed by the evidence presented in this work, caution is needed in inferring a causative role for HCV infection in the aetiopathogenesis of LP. However, some studies have investigated the putative pathological basis for such a hypothesis: HCV antigens and RNA[46,47] have been found in LP tissue by some authors, although negative results have also been reported,[48] and HCV-specific T cells have recently been demonstrated in oral mucosa affected by LP.[49]

We conclude that it seems reasonable to test the sera of patients affected by LP for anti-HCV antibodies, as suggested by other authors,[18] and that the reasons underlying such an association need to be better investigated by both epidemiological studies and basic scientific experiments.

Acknowledgments

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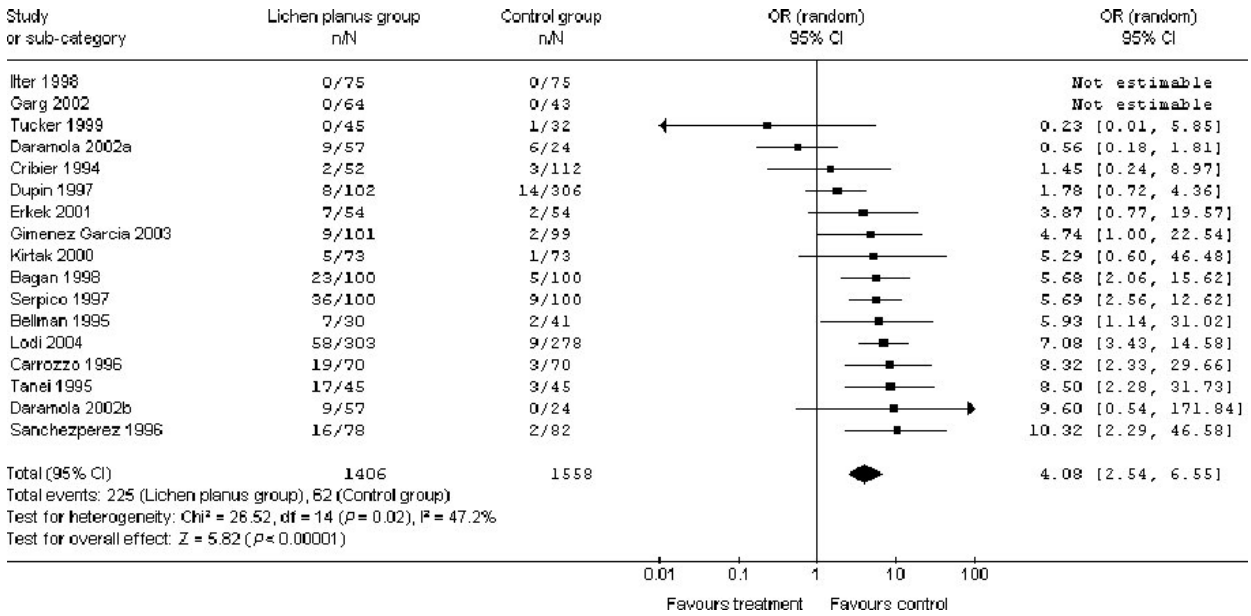

Figure 4. Sensitivity analysis. The odds ratio (OR) was calculated excluding studies with high risk of bias. CI, confidence interval.

Table 4. Hepatitis C virus (HCV), prevalence rates based on published reports[37]

Country	HCV prevalence (%)
Brazil	2·6
France	1·1
Egypt	18·1
Germany	0·1
Italy	0·5
Japan	2·3
Nepal	0·6
Nigeria	1·4
Spain	0·7
Thailand	5·6
Turkey	1·5
U.K.	0·02
U.S.A.	1·8

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