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REVIEW ARTICLE

Hypertension in oral lichen planus: A systematic review and meta-analysis

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Abstract

Objectives: To perform a systematic review and meta-analysis in order to qualitatively and quantitatively evaluate the prevalence and magnitude of the association of hypertension in patients with oral lichen planus (OLP).

Methods: MEDLINE, Embase, Scopus, and Web of Science databases were searched for studies published before May 2022, not restricted by publication language or date. The methodological quality and risk of bias of primary-level studies were critically assessed. Meta-analyses were performed, as well as meta-regression, stratified, sensitivity and small-study effects analyses, a Galbraith (radial) plot, and trial sequential analysis. Quality of evidence was evaluated using GRADE system.

Results: 104 studies, including 16,587 patients, met the inclusion criteria. The results show that patients who suffer from OLP have a high prevalence of hypertension (PP = 24.17%, 95% CI = 21.45–27.00), with a low quality of evidence. A significant association between hypertension and oral lichen planus was also reported (OR = 1.28, 95% CI = 1.01–1.63, $p = 0.04$), showing a moderate quality of evidence.

Conclusions: Patients with OLP could be at an increased risk of suffering from hypertension which is probably due to multiple factors. Healthcare practitioners involved in OLP management should be aware of this comorbidity in order to apply suitable measures and make referrals if hypertension is suspected, although further research is needed.

KEYWORDS
hypertension, lichen planus, oral, meta-analysis, prevalence, systematic review

1 | INTRODUCTION

Oral lichen planus (OLP) is considered to be an autoimmune disease of unknown etiology, in which there is a T-lymphocyte-mediated response to unknown antigens located in the basal and parabasal layers of the oral mucosal epithelium (Gonzalez-Moles & Ramos-García, 2022; Sugerman et al., 2002). It is a chronic and incurable process that is now categorized as a potentially malignant oral disorder, which implies that patients with OLP are at significant risk of developing oral cancer in the course of its evolution (González-Moles, Ramos-García, & Warnakulasuriya, 2021a; González-Moles et al., 2019; González-Moles & Ramos-García, 2021; Ramos-García et al., 2021; Warnakulasuriya et al., 2021). OLP is a disease that affects more than 1% of the general population, with a significant

and progressively higher prevalence after the age of 40; significant geographical differences have been identified regarding its prevalence, being Europe the worldwide area with the highest prevalence (1.32%) while India is the place in the world where OLP is the least frequent (0.49%) (González-Moles, Warnakulasuriya, et al., 2021). It has been recently demonstrated, based on evidence, that OLP is significantly associated with emotional disorders, especially depression, anxiety, and stress (De Porras-Carrique et al., 2021), autoimmune diseases such as hypothyroidism and diabetes (De Porras-Carrique et al., 2022), and liver diseases that predispose to the development of hepatocellular carcinoma, such as hepatitis B and C, liver cirrhosis and steatohepatitis (González-Moles et al., 2020). Some primary-level studies – case series – show that patients with OLP may also develop hypertension (Aguirre-Urizar et al., 2020; Conrotto et al., 2018; Kragelund et al., 2009; Radic et al., 2022) which is relevant because of the serious health related complications, including cardiovascular disease and renal impairment (Oparil et al., 2018). However, despite the potential association of hypertension in patients with OLP, there are no focused systematic reviews and meta-analyses available.

Given the important potential implications to clinical practice, we performed a systematic review and meta-analysis aimed at qualitatively and quantitatively assessing the prevalence and magnitude of the association of hypertension in patients with OLP.

2 | MATERIALS AND METHODS

2.1 | Framework design

This systematic review and meta-analysis followed the criteria based on the Joanna Briggs Institute for Systematic Reviews (University of Adelaide, Australia) (Aromataris & Munn, 2020) and *Cochrane Collaboration* (Higgins & Green, 2008). The study was also designed, conducted, and validated according to AMSTAR2 high standards (Shea et al., 2017), and reported in accordance with PRISMA (Page et al., 2021) and MOOSE (Stroup et al., 2000) statements.

2.2 | Protocol

A protocol was designed a priori and then it was submitted to an internationally well-known database (PROSPERO; www.crd.york.ac.uk/PROSPERO; registration code CRD42023412800) to minimize bias. This protocol was reported to ensure compliance with the PRISMA-P declaration.

2.3 | Search strategy

The following databases were explored for registers published before May 2022: MEDLINE (through PubMed), Embase, Scopus, and Web of Science. In order to maximize sensitivity, searches combined thesaurus and free terms (Table S1, Appendix S1). "Oral lichen planus" was used as the only keyword to find as many studies as possible investigating OLP. With the aim of expanding the search strategy, Google Scholar and handsearching methods were used. All records were managed with the software Mendeley v.1.19.4 (Elsevier).

2.4 | Eligibility criteria

The inclusion criteria were the following: (1) primary-level studies, without publication date or language restrictions; (2) analysis of the prevalence of hypertension in OLP patients (with or without control group), and/or the magnitude of association; (3) observational study design; (4) when results derived from the same study population, the most recently reported or those providing more datasets were included.

The exclusion criteria were the following: (1) retracted articles, reviews, comments, letters, editorials, personal opinions, case reports, meeting abstracts, or book chapters; (2) preclinical studies (e.g., in vitro or animal experimentation, etc.); (3) absence of apparently healthy control group (only applied for the magnitude of association analysis); (4) lack of essential prevalences datasets; (5) Oral lichenoid reactions were also excluded and not considered as OLP.

2.5 | Study selection process

Two authors (TDPC, PRG) individually applied the eligibility criteria. The evaluators, trained and calibrated, performed respective screening rounds to identify and select the included studies. The selection of articles was carried out in two phases: (1) screening of titles and abstracts; (2) full-text reading. Only the studies that met the inclusion criteria were finally selected.

2.6 | Data extraction

One author (TDPC) independently extracted data from the included articles using Excel v.16.46 spreadsheets (Microsoft) and another author (PRG) crosschecked all datasets. All discrepancies were also solved by consensus. The following data was collected from the included studies: (1) first, last, and corresponding author; (2) publication language (non-English language studies were translated using Google Translator); (3) publication year; (4) country and continent; (5) source of patient recruitment; (6) recruitment and follow-up periods; (7) sample size; (8) absolute and relative frequencies of hypertension; (9) study design; (10) location and clinical appearance of lesions; (11) diagnostic criteria for OLP and hypertension; (12) specialists implied; (13) sex, age, and tobacco and alcohol consumption.

2.7 | Appraisal of quality and risk of bias of primary-level studies

The methodological quality and risk of bias of the included primary-level studies were appraised by two authors (TDPC and PRG) using a specific method for systematic reviews addressing prevalence questions and for proportion meta-analyses (Joanna Briggs Institute, University of Adelaide, Australia) (Aromataris & Munn, 2020).

2.8 | Statistical analysis

We extracted proportions (patients with hypertension as numerator/patients with OLP as denominator) given as percentage and they were pooled to their respective 95% confidence intervals (CI) to calculate the prevalence of hypertension in patients suffering from OLP. Freeman-Tukey double-arcsine transformed proportions were computed, in order to stabilize the variance of the study-specific prevalence (Freeman & Tuckey, 1950). The magnitude of the association between OLP and hypertension was also explored by estimating and pooling odds ratios (OR) with their corresponding 95% CI. Random-effects models were used to carry out all meta-analyses in this study weighed by the inverse-variance based on the DerSimonian and Laird method (DerSimonian & Laird, 1986), to consider the possibility of finding different outcomes among study subpopulations (e.g., differences in continents, sex). These results were graphically represented by forest plots ($p < 0.05$ was considered as significant). Heterogeneity between studies was evaluated using the χ-based Cochran's Q test ($p < 0.10$ was considered significant). Also, the I^2 statistic (interpreting values of 50–75% as moderate-high degree of inconsistency across the studies) was assessed to estimate what proportion of the variance in observed effects reflects variation in true effects, rather than sampling error (Higgins et al., 2003; Higgins & Thompson, 2002). Also, we performed preplanned stratified meta-analyses in order to identify possible sources of heterogeneity and to determine subgroups-specific prevalence (Borenstein & Higgins, 2013). Moreover, meta-regression analyses were carried out to explore the potential effect of study covariates on the prevalence of hypertension in OLP. Univariate meta-regressions were performed using the restricted maximum likelihood (REML) method (Thompson & Sharp, 1999). For all meta-regression analyses, we re-calculated p values using Monte Carlo simulations (up to 10,000 permutations per meta-regression) due to the lack of observations (Higgins & Thompson, 2004). To graphically depict these results, we constructed weighted bubble plots. A Galbraith (radial) plot was also constructed to further examine the contributions of individual primary-level studies to the heterogeneity metrics. In addition, sensitivity analyses were carried out to test the reliability of meta-analytical results and to explore the influence of each individual study on the final estimations for each meta-analysis performed. For this, the meta-analyses were repeated sequentially, omitting one study at a time ("leave-one-out" method). Furthermore, funnel plots were constructed and the Egger regression test (performing a linear regression of the effect estimates on their standard errors, weighting by 1/[variance of the effect estimate], considering $p < 0.10$ as significant) was applied in order to asses small-study effects. Finally, trial sequential analysis (TSA) was also carried out, using a specific software (TSA v.9.5.10 Beta, developed by The Copenhagen Trial Unit), in order to provide further information on the precision and conclusiveness of meta-analytical results. The required information size (RIS) was calculated with the assumption of a maximum type I error of 5%, a maximum and a type II error of 20% (80% power). The α-spending function was adopted with O'Brien-Fleming monitoring boundaries computation. A model-variance-based approach was implemented for heterogeneity correction on the basis of meta-analytical findings. In addition, primary-level studies were considered at low/high risk of bias on the basis of the specific appraisal of quality. TSA results were plotted and visual inspection analysis was performed to control if the cumulative Z-curve crossed the RIS threshold, the futility area, and/or the trial sequential monitoring curves for conservative statistical significance. All other statistical analyses were performed with Stata 16.1 (Stata Corp).

2.9 | Evaluation of quality of evidence

Two authors (TDPC and PRG) evaluated the quality of evidence using the "*Grading of Recommendations Assessment, Development and Evaluation*" GRADE system (Guyatt et al., 2008; https://www.gradeworkinggroup.org). According to GRADE, the quality of evidence is classified into one of four levels: very low, low, moderate, or high. An initial baseline of overall high-quality evidence was assigned. Then, that overall quality rating was "downgraded" based on the following domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias (Guyatt et al., 2008). No outcome was "upgraded" according to other criteria, for example, magnitude of effect size. Discrepancies were resolved by consensus.

3 | RESULTS

3.1 | Literature search

The flow diagram (Figure 1) exhibits the selection process in which 14,138 studies, published before May 2022, were retrieved: 3743 from PubMed, 3604 from Embase, 3224 from Web of Science, 3565 from Scopus and two from handsearching methods. 5289 titles and abstracts were screened once the duplicate studies were eliminated. 115 studies were then full-text read and, of these, 104 were included (Appendix S1). The list of excluded studies in the second phase is available in the Appendix S1.

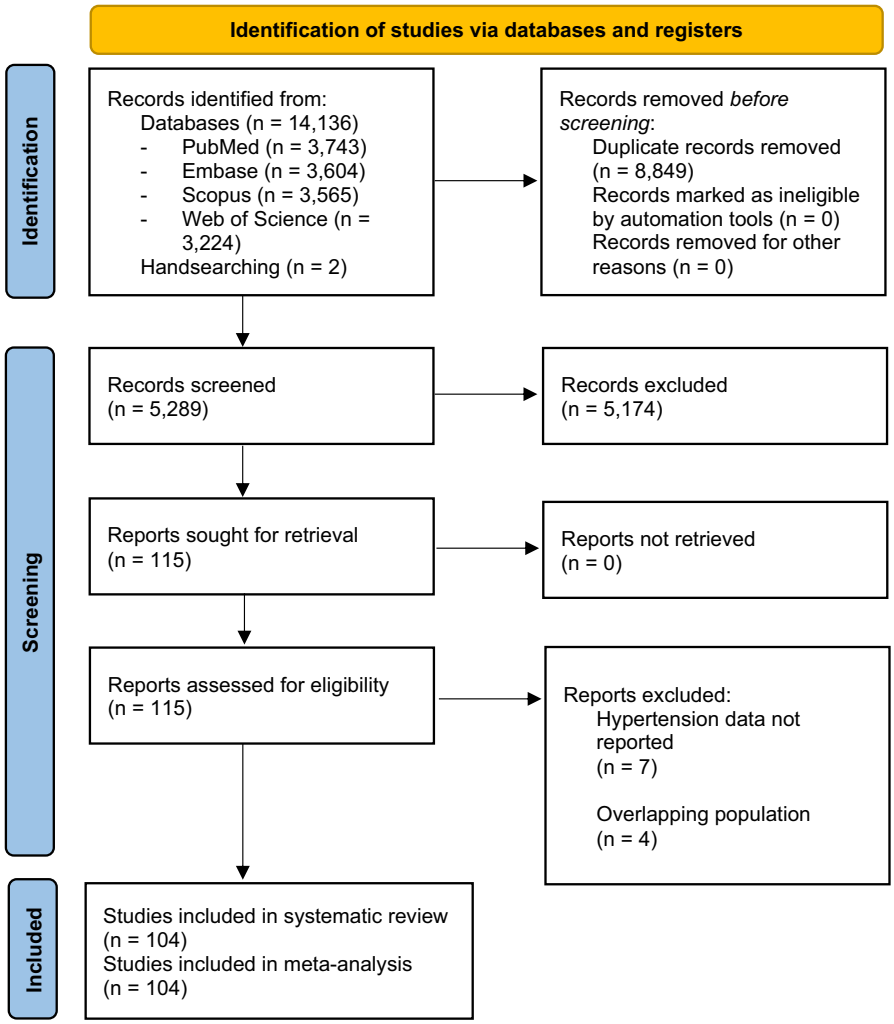

FIGURE 1 Flow Diagram showing the identification and selection process of studies that address the prevalence of hypertension among OLP patients.

3.2 | Study characteristics

Table 1 summarizes the general characteristics of the 104 meta-analyzed studies, which recruited 16,587 patients. With respect to the prevalence by continents, 47 studies (7752 patients) were conducted in Asia, 33 studies (5606 patients) in Europe, nine studies (1764 patients) in North America, seven studies (377 patients) in South America, and there was only one study (53 patients) carried out in Oceania. Seven studies (1035 patients) took place across multiple continents. Studies carried out in different languages were also found, with English being the predominant language in 98 studies (15,678 patients). Three studies (136 patients) were conducted in Italian, and only one study was found in French (nine patients), Chinese (724 patients), and Russian (40 patients). Table S2 shows the characteristics of these studies in detail (Appendix S1).

TABLE 1 Characteristics of the studies included in the meta-analysis.

Total studies	104
Publication year	1989–2022
Sample size	
Total no. patients	16,587
Range	6–808
Geographic area	
Asia	47 studies (7752 patients)
Europe	33 studies (5606 patients)
North America	9 studies (1764 patients)
South America	7 studies (377 patients)
Oceania	1 studies (53 patients)
Global	7 studies (1035 patients)
Language	
English	98 studies (15,678 patients)
Italian	3 studies (136 patients)
French	1 study (9 patients)
Chinese	1 study (724 patients)
Russian	1 study (40 patients)

3.3 | Qualitative evaluation

The results of the risk of bias (RoB) analysis are illustrated in the Quality plot (Figure 2). Items Q2, Q9, and Q10 harbored the

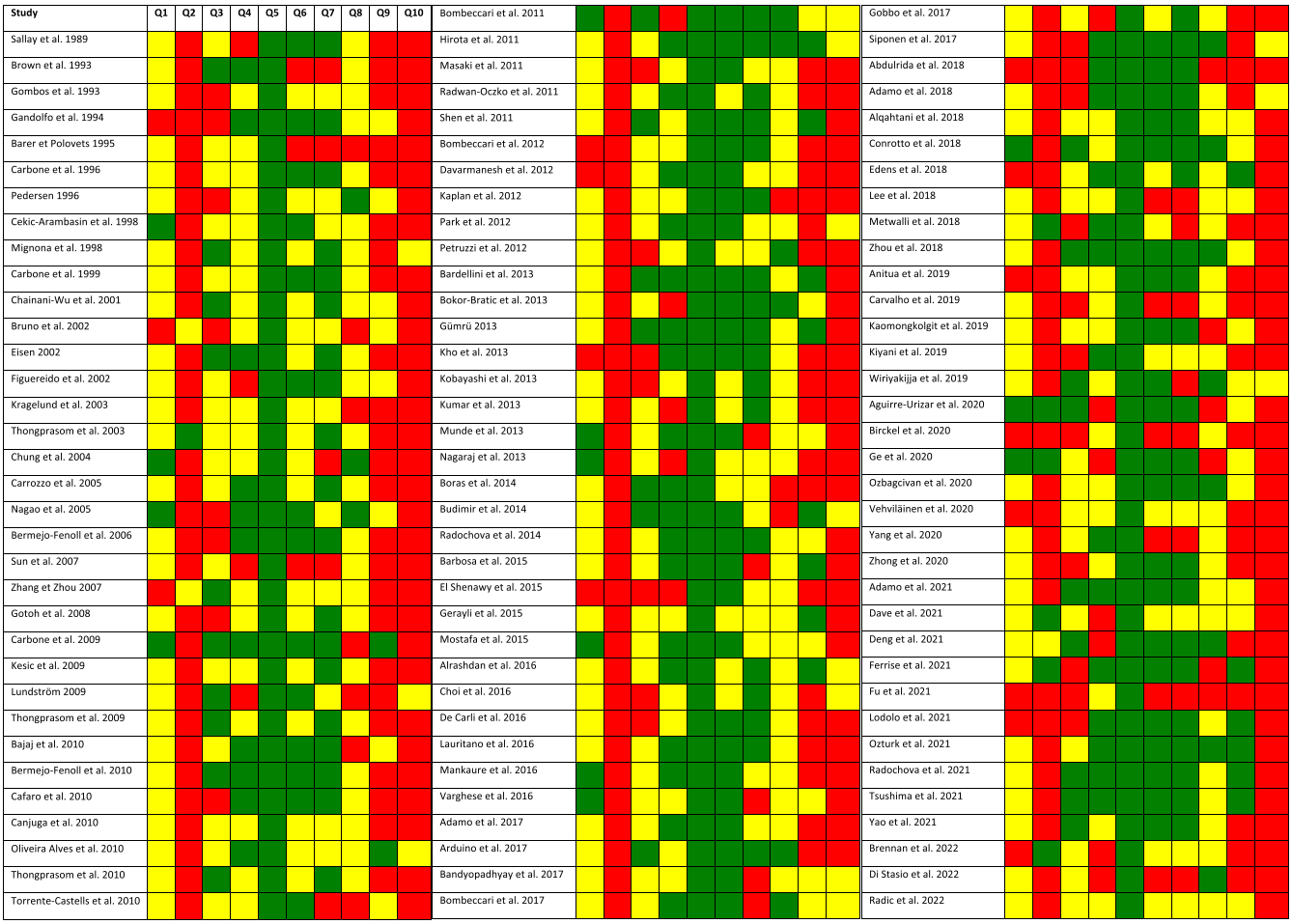

FIGURE 2 Quality Plot depicting the risk of bias in individual studies, critically appraising 10 domains, using a method specifically designed for systematic reviews addressing questions of prevalence and for proportion meta-analyses (developed by Joanna Briggs Institute, University of Adelaide, South Australia). The following domains were scrupulously evaluated: (1) Was the target population represented by the study subjects?; (2) Was the study sample recruited randomly?; (3) Was there a sample size calculation?; (4) Was the clinical setting and sample population thoroughly detailed?; (5) Was the coverage of the data analysis sufficient for the identified sample?; (6) Were objective and standardized criteria used for the diagnosis of OLP?; (7) Were the measurement criteria accurate?; (8) Was the statistical analysis conducted adequate?; (9) Were all confounding factors (type of lichenoid lesion/reaction, definition and/or characterization of alcohol and tobacco consumption and mean age) reported and considered?; and (10) Were subpopulations properly identified? The items were individually classified as "No" (High RoB), "Uncertain" (mild RoB), and "Yes" (low RoB). Moreover, with the purpose of obtaining a global RoB result, every item was assigned to a particular score (high RoB = 1; moderate RoB = 2; low RoB = 3).

highest risk of potential bias. The Q2 item investigates the adequate recruitment of patients in each study. The Q9 item focuses on biases due to the lack of control of potentially confounding factors in the studies. Lastly, the Q10 item evaluates the data report from the study subpopulations (sex, age, alcohol, and tobacco consumption).

3.4 | Quantitative evaluation (meta-analysis)

The results of the statistical analyses are represented in detail in Tables 2 and 3, graphically depicted by forest plots, bubble plots, sensitivity interval plots, Galbraith (radial) and TSA plots (Figures 3 and 4; Appendix S1). The meta-analysis on the prevalence of hypertension in patients with OLP showed a pooled proportion of 24.17% (95% CI = 21.45–27.00), with a considerable heterogeneity degree ($I^2 = 93.17\%$, $p < 0.001$). The meta-analysis on the magnitude of association showed a significant association between OLP and hypertension, with low to moderate statistical heterogeneity (OR = 1.28, 95% CI = 1.01–1.63, $p = 0.04$; $p_{het} = 0.02$, $I^2 = 46.3\%$), deriving this result from a meta-analyzed sample of 17 out of the 107 (15.89%) primary-level studies included in the present systematic review. The individual contributions to statistical heterogeneity metrics were further explored by constructing a Galbraith (radial) plot (Figure 4), showing that few specific primary-level studies ($n = 3$) contributed substantially in comparison to the rest of the meta-analyzed sample. Nevertheless, salient characteristics were not found, so potential sources of heterogeneity could not be identified through this analysis.

TABLE 2 Prevalence of hypertension in patients with OLP and associated factors.

	Sample size (*n*)		Statistical		Pooled data		Heterogeneity	
Meta-analyses	Studies	Patients	Model	Method	ES (95% CI)	*P*-value	P_{het}	I^2 (%)
Prevalence[a]	104	16,587	REM	D-L	PP = 24.17% (21.45–27.00)	–	<0.001	93.17
Prevalence by continent[b]								
Europe	33	5606	REM	D-L	PP = 27.39% (23.55–31.39)	<0.001[c]	<0.001	92.00
Asia	47	7752	REM	D-L	PP = 17.24% (14.03–20.69)		<0.001	87.29
South America	7	377	REM	D-L	PP = 28.68% (19.93–38.23)		0.01	66.59
North America	9	1764	REM	D-L	PP = 26.37% (15.42–38.96)		<0.001	96.25
Oceania	1	53	REM	D-L	PP = 13.21% (6.55–24.84)		–	–
Global	7	1035	REM	D-L	PP = 26.00% (17.76–35.15)		<0.001	87.37
Prevalence by sex[b]								
Females	28	2188	REM	D-L	PP = 23.58% (17.87–29.73)	0.68[c]	<0.001	83.94
Males	28	1029	REM	D-L	PP = 18.84% (13.25–24.95)		<0.001	54.16
Prevalence by Immunosuppresion therapy[b]								
No	8	314	REM	D-L	PP = 26.05% (18.10–34.78)	0.38[c]	0.03	55.60
Yes	25	4373	REM	D-L	PP = 22.35% (17.25–27-88)		<0.001	93.60
Prevalence. Univariable meta-regression[d]								
Age (mean age of patients)	92	13,893	Random-effects Meta-regression		Coef = 0.010 (0.006 to 0.015)	<0.001[e]	–	–
Tobacco (% of smokers)	51	8658	**Random-effects Meta-regression**		Coef = .001 (−0.002 to 0.003)	0.66[e]	–	–
Alcohol (% of drinkers)	34	6201	Random-effects Meta-regression		Coef = 0.003 (0.001 to 0.005)	0.02[e]	–	–
Red lesions (% of OLP patients)	72	9173	Random-effects Meta-regression		Coef = −0.000 (−0.002 to 0.001)	0.75[e]	–	–
RoB	104	16,587	Random-effects%%Meta-regression		Coef = −0.000 (−0.014 to 0.012)	0.93[e]	–	–

Abbreviations: CI, confidence intervals; D-L, DerSimonian and Laird method; OLP, oral lichen planus; PP, pooled proportion; REM, random-effects model; RoB, risk of bias; Stat., statistical; Wt, method of weighting.

[a]Proportion meta-analyses.

[b]Proportion meta-analyses (Subgroup analyses).

[c]Test for between-subgroup differences.

[d]Effect of study covariates on the prevalence of hypertension among OLP patients. A meta-regression coefficient >0 indicates a greater impact of covariates on the prevalence of hypertension in patients with OLP.

[e]*p*-value recalculated after 10,000 permutations based on Montecarlo simulation.

3.5 | Subgroup meta-analysis and meta-regression

Subgroup meta-analyses stratified by geographical area, sex and use of immunosuppresive therapy were applied to the prevalence analysis, showing only significant differences between continents ($p < 0.001$). Europe was the continent that showed the highest prevalence of hypertension among OLP patients (PP = 27.39%, 95% CI = 23.55–31.39). This result was also maintained for Europe (OR = 1.56, 95% CI = 1.2–1.99, $p = 0.001$) in the subgroup meta-analysis applied to the magnitude of association analysis (Tables 3 and 4, Appendix S1). The rest of subgroup meta-analyses could not be applied due to the low number of observations provided across primary-level studies. Univariable meta-regressions were also performed to explore the potential effect of the study covariates age, tobacco, alcohol, OLP clinical type and risk of bias on the prevalence of hypertension in OLP patients. A significant effect was found for the covariates age ($p < 0.001$) and alcohol ($p = 0.02$) on the prevalence analysis. But none of these covariates showed significant differences when meta-regressions were applied to magnitude of association analysis (Tables 3 and 4, Appendix S1). The results of these secondary analyses were difficult to interpret and seem inconclusive, as they derive from subgroups with few patients, limited observations and inconsistent results. More investigation is needed to obtain evidence-based results on these potential study subpopulations, without a clear current potential for translation to clinical practice.

TABLE 3 Magnitude of association between hypertension and OLP.

	Sample size (n)		Statistical		Pooled data		Heterogeneity	
Meta-analyses	Studies	Patients	Model	Method	ES (95% CI)	*p*-value	P_{het}	I^2 (%)
Magnitude of association[a]	17	5272	–	–	OR = 1.28 (1.01–1.63)	0.04	0.02	46.30
Magnitude of association by continent[b]						0.003[c]		
Europe	6	2079	REM	D-L	OR = 1.56 (1.21–1.99)	0.001	0.252	24.30
Asia	6	2473	REM	D-L	OR = 0.98 (0.72–1.35)	0.92	0.422	<0.001
South America	2	201	REM	D-L	OR = 0.81 (0.44–1.50)	0.51	0.670	<0.001
North America	2	327	REM	D-L	OR = 1.38 (0.89–2-13)	0.15	0.769	<0.001
Global	1	192	REM	D-L	OR = 92.53 (5.36–1598.13)	0.002	–	–
Magnitude of association. Univariable meta-regression[d]								
Age (mean age of patients)	15	3586	Random-effects Meta-regression		Coef = 0.017 (−0.027 to 0.062)	0.55[e]	–	–
Tobacco (% of smokers)	12	3748	Random-effects Meta-regression		Coef = 0.002 (−0.030 to 0.035)	0.84[e]	–	–
Alcohol (% of drinkers)	8	2685	Random-effects Meta-regression		Coef = 0.005 (−0.044 to 0.055)	0.79[e]	–	–
Red lesions (% of OLP patients)	10	2375	Random-effects Meta-regression		Coef = −0.000 (−0.015 to 0.016)	0.88[e]	–	–
RoB	17	5272	Random-effects Meta-regression		Coef = −0.007 (−0.131 to 0.145)	0.89[e]	–	–

Abbreviations: CI, confidence intervals; D-L, DerSimonian and Laird method; OLP, oral lichen planus; PP, pooled proportion; REM, random-effects model; RoB, risk of bias; Stat., statistical; Wt, method of weighting.

[a]Magnitud of association meta-analyses.

[b]Magnitud of association meta-analyses (Subgroup analyses).

[c]Test for between-subgroup differences.

[d]Effect of study covariates on the magnitude of association between OLP and hypertension. A meta-regression coefficient >0 indicates a greater impact of covariates on the magnitude of association.

[e]*p*-value recalculated after 10,000 permutations based on Montecarlo simulation.

3.6 | Sensitivity analysis

The results of the sensitivity analysis – jointly with the visual inspection analysis of the Galbraith plot – rule out the presence of outliers contributing disproportionately to the overall results of the meta-analysis. However, the leave-one-out method also confirmed – jointly with the visual inspection analysis of TSA plot – that results were not stable, substantively changing after the sequential repetition of meta-analyses with loss of conventional statistical significance after the omission of certain studies.

3.7 | Analysis of small-study effects

As suspected through the funnel plot (Appendix S1), Egger's regression test points out statistically significant asymmetry for the prevalence of hypertension in patients with OLP ($p_{Egger} = 0.08$). However, the visual inspection analysis of the asymmetry of the funnel plot on the magnitude of association between hypertension and OLP, and the statistical test conducted for the same purpose (*p*-Egger = 0.98; Appendix S1) potentially ruled out the presence of publication bias.

3.8 | Trial sequential analysis (TSA)

The last Z-curve point outside of the RIS area crosses the conventional significance line, and the next added study sits in contact with the lower monitoring boundary. Therefore, visual inspection analysis of TSA plot (Figure 4) confirms the potential association between OLP and hypertension. Nevertheless, TSA also shows that current evidence is not firm enough due to the imprecision inherent to the following added studies. So, these meta-analytical findings should be considered inconclusive from a conservative approach, and future primary studies with better methodological quality are needed.

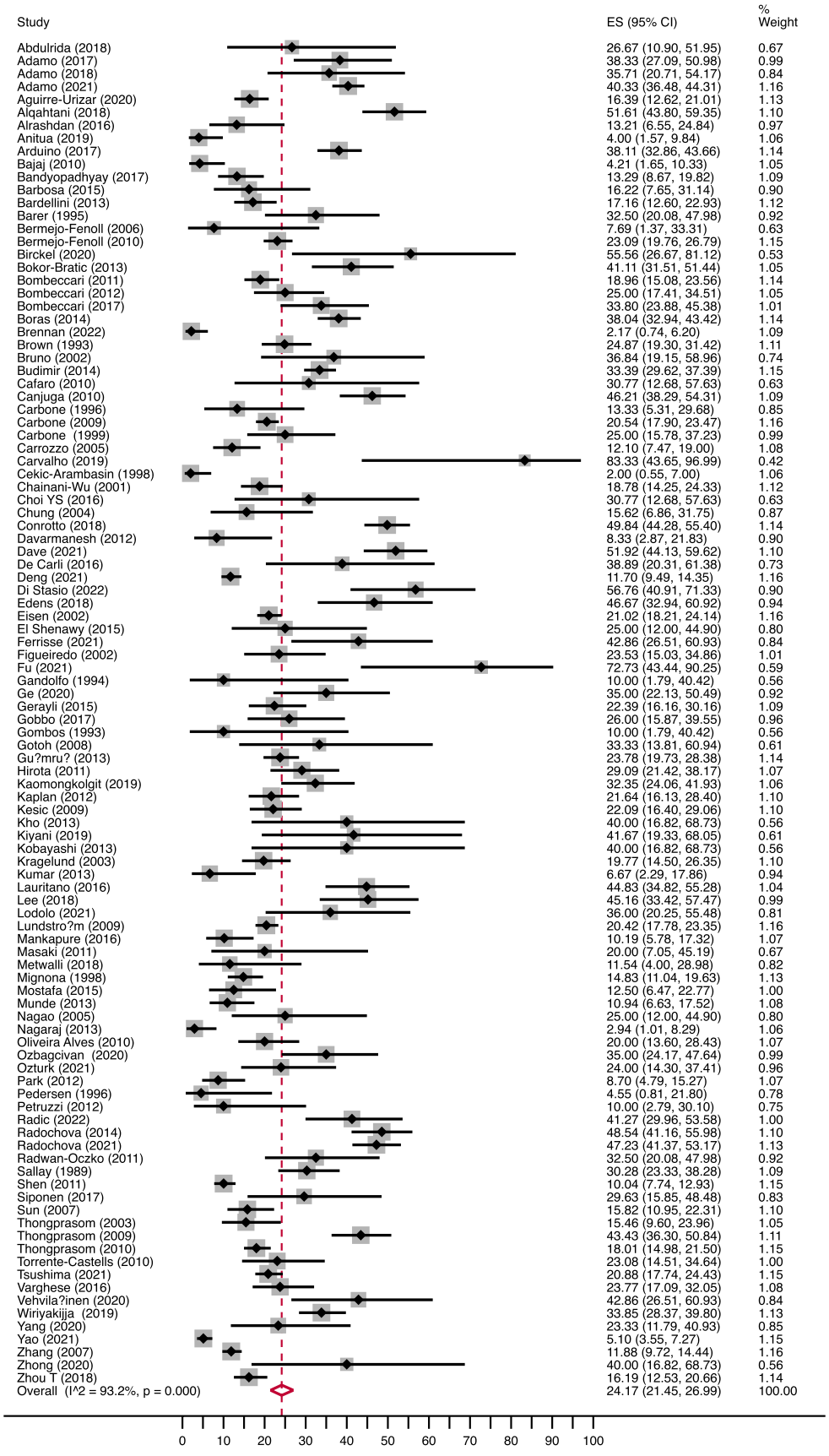

FIGURE 3 Forest Plot graphically representing the meta-analysis on the prevalence of hypertension in patients with OLP. Random-effects model, DerSimonian and Laird method. Pooled proportions (expressed as percentage) were used as ES measure. CI, confidence intervals; ES, effect size.

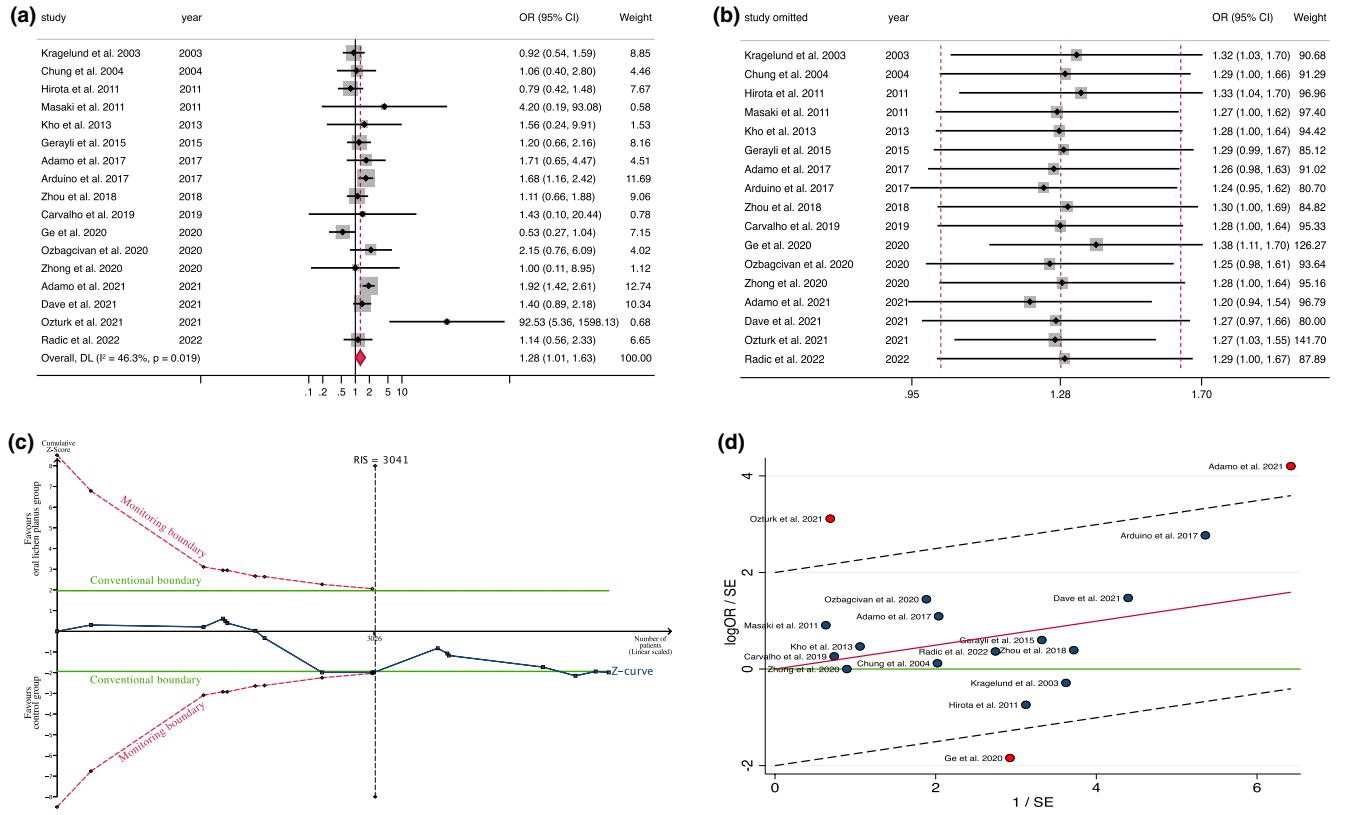

FIGURE 4 (a) Forest plot graphically representing the meta-analysis of the magnitude of association between hypertension and OLP. Random-effects model, DerSimonian and Laird method. OR and 95% CI were used as effect size metric. OR, odds ratio; CI, confidence intervals; OLP, oral lichen planus. (b) Interval plot graphically representing the sensitivity analysis of the studies pooled in the meta-analysis on the magnitude of association between hypertension and OLP. The "leave-one-out" method was applied, sequentially omitting one study at a time to investigate its influence on the overall meta-analytical result. In the interval plot, the usual diamond shape representing the pooled effect was replaced by vertical intermittent red lines. OR, odds ratio; CI, confidence intervals; OLP, oral lichen planus. (c) TSA on the magnitude of association between OLP and hypertension, performed to investigate the precision and conclusiveness of meta-analytical results. The vertical axis represent the cumulative Z-score against the additive number of patients on the horizontal axis. The Z-curve (blue line) is projected from the origin (0,0), the RIS threshold (intermittent black line) calculates the optimal number of patients ($n = 3041$), two horizontal lines define the conventional significance levels (green lines; $z = \pm 1.98$), and two O'Brien-Fleming curves (intermittent red lines) define the trial sequential monitoring boundaries for conservative statistical significance. OLP, oral lichen planus; RIS, required information size; TSA, trial sequential analysis. (d) Galbraith (radial) plot of the magnitude of association between hypertension and OLP, constructed to examine the contributions of individual studies to the heterogeneity metrics. The vertical axis represents the observed effect sizes standardized by their corresponding standard errors ($y = \text{logOR/SE[logOR]}$) against precision on the horizontal axis ($x = 1/\text{SE[logOR]}$). The regression diagonal dark red line is projected from the origin (0,0), and the approximate 95% confidence intervals run between the two intermittent parallel lines at ±2 units above and below the regression line. The studies inside this 95% confidence region were represented as dark blue circles. The studies located slightly above and below the confidence limits (outside the grey region, depicted as red circles) contribute substantially to the observed heterogeneity. OLP, oral lichen planus; OR, odds ratio; SE, standard error.

3.9 | Quality of evidence

According to GRADE system (Table 4), there was a "low" quality of evidence for the outcome prevalence of hypertension in patients with OLP, and "moderate" quality of evidence for the magnitude of association outcome. The most influential domain to obtain this certainty rating was "Indirectness" for both outcomes critically judged. Most primary-level studies were considered as sources of indirect evidence. This means, in pragmatic terms, that these studies were not originally focused to investigate the target outcomes in this systematic review.

4 | DISCUSSION

The results of this systematic review and meta-analysis on 104 studies and 16,587 patients with OLP show a prevalence of hypertension of 24.17% in these patients, which was significantly higher in comparison to the prevalence found in the control group of patients without OLP (OR = 1.28, $p = 0.04$). There is insufficient evidence on the reasons for this increased prevalence of hypertension in OLP. A hypothetical justification could be related to an adverse effect of corticosteroid treatment frequently used to manage OLP. However, it has not been revealed a higher

TABLE 4 Evaluation of quality of evidence using Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

Outcome	No of studies	No of patients	ES (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence
Prevalence of hypertension in patients with OLP	104	16,587	PP = 24.17% (21.45–27.0)	Not serious	Serious	Serious	Not serious	Not serious	⊕⊕◯◯ LOW
Magnitude of association between hypertension and OLP	17	5272	OR = 1.28 (1.01–1.63)	Not serious	Not serious	Serious	Not serious	Not serious	⊕⊕⊕◯ MODERATE

Note: Scoring system: An initial baseline overall quality of "high quality" of evidence was assigned to the outcome under analysis. Then, this rating is "downgraded" based on the following domains: risk of bias, inconsistency, indirectness and imprecision (overall quality of evidence rating was not "upgraded" according to any criteria, e.g., magnitude of effect size). The quality of evidence is classified in one of four levels: very low, low, moderate or high. A "serious" score downgrades one level of evidence, "very serious" two levels. Although "large effect size" upgrades one level of evidence, no variables were considered for upgrading. Risk of bias: Quality was assessed according to the risk of bias analysis performed using JBI tool and after univariable meta-regression analyses. Inconsistency: Heterogeneity was assessed via Q-test and I^2 statistic. $I^2 > 50\%$ and Q test p-values ≤ 0.10 were considered as significant heterogeneity and a "serious" rating was assigned. Indirectness: According to our critical judgment and knowledge, all outcomes were considered as sources of indirect evidence (i.e., a research that does not directly compare the exposures or effects which we are interested in, target subpopulations and/or outcomes of interest). Imprecision: Narrow confidence intervals and large enough sample sizes ("rule of thumb" ≥10 studies) were present. Furthermore, TSA analysis confirmed that the required number of patients was recruited for the magnitude of association meta-analysis. Publication bias: If publication bias was strongly suspected, it was recorded for descriptive purposes. Nevertheless, due to the lack of consensus on the influence of publication bias in meta-analyses of proportions, this domain was not rated nor considered for downgrading. GRADE certainty ratings. Very low: The true effect is probably markedly different from the estimated effect; Low: The true effect might be markedly different from the estimated effect; Moderate: The authors believe that the true effect is probably close to the estimated effect; High: The authors have a lot of confidence that the true effect is similar to the estimated effect.

Abbreviations: CI, confidence intervals; JBI, Joanna Briggs Institute; OLP, oral lichen planus; OR, odds ratio; PP, pooled proportions; TSA, trial sequential analysis.

frequency of hypertension in those case series that used immunosuppression for disease control compared to studies in which patients with OLP were not treated with immunosuppressants. Although it is not possible to extract from the primary level studies, due to the lack of individualized information, what type of immunosuppressants were used in each series, it is to be expected that topical corticosteroids are the first choice for the treatment of OLP. It is known that systemic corticosteroid therapy can generate increased blood pressure as an adverse effect secondary to sodium and fluid retention (González-Moles & Scully, 2005; Jackson et al., 1981; Shen & Young, 2012); however, there is limited scientific evidence that this adverse reaction can also happen with the use of topical corticosteroids (Carbone et al., 2003). It has been indicated that the higher frequency of hypertension in patients with OLP is not due to the effect of immunosuppressants, most likely topical or systemic corticosteroids, so other reasons could underlie the association of OLP and hypertension.

We have previously reported a higher prevalence of some important diseases in OLP patients. These include some psychological disorders, essentially depression, anxiety, and stress (De Porras-Carrique et al., 2021). There is clear evidence of the relationship between depression and hypertension (Li et al., 2015; Scalco et al., 2005), such as the hypertension-inducing capacity mediated by anxiety and stress, which is probably linked to autonomic hyperactivity with increased production of circulating catecholamines (Gasperin et al., 2009; Johnson, 2019; Light et al., 1983; Yan et al., 2015). OLP patients, on the other hand, also have a significantly higher prevalence of autoimmune diseases (De Porras-Carrique et al., 2022), including the hypothyroidism secondary to autoimmune destruction of the thyroid gland. Severe hypothyroidism generates fluid and sodium retention, with a state of volume depletion, low osmolarity in the extracellular compartment and increased water retention with increased peripheral vascular resistance, which constitutes a possible link between this disease and hypertension (Chaker et al., 2018; Saito et al., 1983; Stabouli et al., 2010). In addition, the evidence accumulation indicates that the chronic inflammatory process that occurs in autoimmune diseases may be responsible for hypertension, and likewise, immune hyperreactivity to HSP70 heat shock proteins could also be involved in the development of hypertension (Di & Gao, 2003; Rodriguez-Iturbe et al., 2023; Sugerman et al., 1995); finally, there is also evidence that T-cells, so relevant in the pathogenesis of OLP, play a role in the development of hypertension (Rodríguez-Iturbe et al., 2014). These mechanisms could hypothetically explain the prevalence of hypertension found in patients with OLP in this study. Meanwhile, we have also reported a higher frequency of diabetes in patients with OLP, both type I and II (De Porras-Carrique et al., 2022; González-Moles & Ramos-García, 2021). Type I diabetes may justify hypertension in OLP both as an autoimmune process and because of the presence of diabetic nephropathy in 30% of patients (Landsberg & Molitch, 2004). The frequency of presentation of metabolic syndrome in patients with type II diabetes may be the explanation for hypertension in patients with concomitant type II diabetes and

OLP (Landsberg & Molitch, 2004). Although the aforementioned causes could reasonably justify the association found in this meta-analysis between OLP and hypertension, the primary level studies evaluated, by not offering individualized patient data, do not allow evidence-based comparisons that point to these OLP-associated diseases as a cause of hypertension in these patients. Clearly, further research is needed in this field, and some of the procedures carried out in the present study show that the quality of the evidence is still low-moderate (GRADE system) and not sufficiently robust (TSA and sensitivity analysis). Overall, these meta-analytical results on a large sample size point to the existence of this comorbidity. So, based on the current evidence, it seems rational that oral medicine and pathology specialists, dentists and other health professionals (e.g., primary-care physicians, dermatologists, etc.) involved in the management of OLP should be aware of this potential comorbidity in order to implement the appropriate measures and referral in case of hypertension suspicion. Geographical differences were also identified regarding the prevalence of hypertension in OLP, being Europe and America the areas with the highest prevalence, as compared to Asia. There could be influences related to lifestyle in Western countries (i.e., stress, diet, …) behaving as favoring factors (Kearney et al., 2004; Mills et al., 2016).

In this systematic review and meta-analysis, oral lichenoid reactions have been intentionally excluded due to their diverse nature as a varied group of oral lesions with well-known causes such as silver amalgam, or drugs (Gonzalez-Moles & Ramos-García, 2022; González-Moles, Ramos-García, & Warnakulasuriya, 2021b). Unlike canonical OLP, oral lichenoid reactions are not considered to be strictly autoimmune in nature. Additionally, while OLP and these reactions share several clinical and pathologic similarities, the addressing of the underlying causes of oral lichenoid reactions often results in their disappearance. Hence, the present study focuses exclusively on "true" OLP cases, based on historical diagnostic criteria that have been employed in primary level studies, in order to avoid a potential distortion on the association between OLP and hypertension.

Based on the qualitative assessment, applying Joanna Briggs Institute's specific critical appraisal checklist for systematic reviews, we found that the methodological quality was variable at both the interstudy and interdomain levels, harboring the highest risk of bias in the domains Q2 (sampling methods not reported), Q9 (confounding factors not considered), and Q10 (no data from study subpopulatios). However, a remarkable fact was that the methodological quality did not seriously affect the results of this study according to the stratified meta-analyses.

Some limitations were also found in this study. Firstly, a considerable degree of statistical heterogeneity was identified in the meta-analysis results. Heterogeneity was accounted by applying a random-effects model to all statistical analyses. Furthermore, some results found in the subgroup meta-analyses and meta-regressions may explain potential sources of heterogeneity. Secondly, the asymmetry observed in the funnel plot did not allow us to rule out the presence of publication bias, a common problem in health sciences related to the tendency to only publish favorable results. Another limitation of the study is related to the fact that only a small fraction of the number of primary-level studies systematically reviewed could be included in the meta-analysis of the magnitude of the association (17 out of 104). This is mainly due to the lack of control group or missing data reported by the studies. Future better-designed primary-level studies should be conducted to adequately serve this purpose. On the other hand, this study presents strengths, such as the large sample investigated, the detection of lines of future research, and promising results on a health problem with relevant consequences for clinical practice.

5 | CONCLUSIONS

In conclusion, patients with OLP could be at an increased risk of suffering from hypertension that is possibly due to multiple factors, including the autoimmune pathogenic substrate of the disease itself, its association with other autoimmune diseases, with depression, anxiety and stress, or with diabetes. Healthcare practitioners involved in OLP management should be aware of this comorbidity in order to apply suitable measures and make referrals if hypertension is suspected, although further research is needed.

AUTHOR CONTRIBUTIONS

Teresa De Porras-Carrique: Writing – review and editing; methodology; conceptualization; software; data curation; investigation; validation; formal analysis; visualization; resources; writing – original draft. **Pablo Ramos-García:** Supervision; writing – review and editing; methodology; conceptualization; software; data curation; formal analysis; validation; investigation; visualization; resources; writing – original draft. **Miguel Ángel González-Moles:** Supervision; writing – review and editing; writing – original draft; conceptualization; methodology; software; data curation; resources; formal analysis; visualization; validation; investigation.

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CONFLICT OF INTEREST STATEMENT

All authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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