Manifestaciones Clínicas del Penfigoide Ocular de las Membranas Mucosas: Revisión Sistemática de la literatura y Meta-análisis

Clinical Characteristics of Ocular Mucous Membrane Pemphigoid: a Systematic Review and Meta-analysis

Trabajo de investigación para optar al título de
ESPECIALISTA EN EPIDEMIOLOGÍA

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ABSTRACT:

Purpose: To synthesize the evidence and generate a combined weighted measure on the frequency of ocular manifestations of mucous membrane pemphigoid (OMMP).

Methods: Systematic literature review and meta-analysis, searching Pubmed, Embase, VHL, and Google Scholar. Articles reporting patients with mucous membrane pemphigoid and ocular involvement were included. At least two reviewers independently and in parallel participated in all the following phases; preliminary screening, full-text review, risk of bias assessment by validated tools, and data extraction. Qualitative analysis and meta-analysis were conducted. This study was previously registered in PROSPERO (CRD42023451844).

Results: Thirty-five studies met the inclusion criteria, comprising 1,439 patients and 1,040 eyes summarized in qualitative analysis. 28 studies were included in the meta-analysis. Ages included ranged from 60.4 to 75 years. Women were reported with more frequency. The mean time for diagnosis was 55.1 months, usually with bilateral ocular disease in 90% (95% CI 78%; 96%). Trichiasis and entropion were the most frequent manifestations in up to 92%, followed by symblepharon and punctate keratitis. Ankyloblepharon, persistent epithelial defects, and visual impairment were less frequent complications. direct immunofluorescence positivity in conjunctival biopsies was 54% (95% CI 43%; 64%). Extraocular involvement was highly frequent, being oral and skin involvement the most frequently reported.

Conclusions: Our systematic review and meta-analysis evidenced that patients around 60 years of age are the most affected population with a female preponderance, usually with bilateral ocular involvement, although visual impairment and persistent epithelial defects were less reported, these clinical findings should not be overlooked in suspected OMMP.

Keywords: Ocular Mucous Membrane Pemphigoid, Ocular Cicatricial Pemphigoid, Mucous Membrane Pemphigoid, Cicatrizing Conjunctivitis

INTRODUCTION:

Mucous membrane pemphigoid (MMP) is a systemic, immune-mediated, chronic disease characterized by the development of subepithelial blisters due to the presence of autoantibodies directed against structural components of the dermal-epidermal junction (1–3). It predominantly compromises mucous membranes and occasionally the skin, with a tendency to scarring and potentially life-threatening complications (1,4,5). Disease presentation and severity vary greatly amongst patients, with nearly 65% - 80% of cases presenting with ocular compromise, ranging from mild conjunctival hyperemia up to chronic bilateral conjunctivitis with remission and reactivation periods (1,6,7). It has been described as predominantly affecting women, in an age range of 60 to 80 years (2,8,9). Although it has been reported to be associated with some immunogenetic phenotypes such as HLA-DBQ1*0301, it has not been associated with a geographic or racial predilection in previous studies (4,10).

The ocular involvement of mucous membrane pemphigoid, properly known as ocular mucous membrane pemphigoid (OMMP), and previously known as ocular cicatricial pemphigoid (OCP), is a rare and poorly understood cause of visual impairment prompted by chronic conjunctival inflammation resulting in scarring, subepithelial fibrosis, tissue remodeling, and neovascularization (1,6). Significant ocular complications, including severe dry-eye syndrome, corneal erosions, corneal keratinization, entropion, and symblepharon, among others, can arise, and progress to irreversible blindness in up to 50% of cases, due to limbal stem cell deficiency (1,2).

Diagnosis of OMMP can be challenging during the initial stages of the disease, due to non-specific early clinical manifestations (1). A thorough medical history and proper evaluation are the basic pillars for an accurate diagnosis, along with the conjunctival biopsy as support for diagnosis, by demonstrating the presence of blisters and linear deposits of IgA, IgG, and C3 in the basement membrane zone through direct immunofluorescence (DIF) or immunohistochemistry (6,11).

Currently, there is no synthesized evidence about the clinical characteristics of ocular manifestations of MMP worldwide. We aim to conduct a systematic literature review and a quantitative analysis of the available evidence to provide an in-depth and pooled frequency of the clinical manifestations of OMMP. This information is useful for healthcare practitioners, mainly ophthalmologists and dermatologists, as they could be informed about baseline disease characteristics, also about less and more common symptoms, so appropriate treatment can be started without delay, contributing to a favorable prognosis.

METHODS:

This systematic review and meta-analysis were conducted following the proposal for reporting Meta-analysis of Observational Studies in Epidemiology (MOOSE) (12) and 'Preferred Reporting Items for Systematic Review and Meta-analysis (the 'PRISMA' statement) (13), both can be found in the **Supplementary Material 1**. PRISMA and MOOSE check list_POC. Previously, this review was registered in PROSPERO under the reference CRD42023451844. This study is based on data available in the public domain and did not use individual-level data, so institutional review board approval was not required.

Search strategy

The following electronic bibliographic databases were searched; PubMed, Embase, Virtual Health Library (VHL), and Google Scholar. MeSH terms, Emtree terms, and DeCS terms were used. The terms were combined with the Harvard Countway Library filter for observational designs (14). The search strategy was first constructed for PubMed and was performed as follows: ("pemphigoid, benign mucous membrane"[MeSH Terms] OR "Mucous Membrane"[MeSH Terms] OR "Ocular Cicatricial Pemphigoid"[Title/Abstract]) AND ("entropion"[MeSH Terms] OR "trichiasis"[MeSH Terms] OR "visual acuity"[MeSH Terms] OR "conjunctivitis"[MeSH Terms] OR ("clinical features"[Title/Abstract] OR "clinical characteristics"[Title/Abstract])) AND ("cohort studies"[MeSH Terms] OR "case-control studies"[MeSH Terms] OR "risk factors"[MeSH Terms] OR "comparative study"[Publication Type] OR "cohort"[Text Word] OR "compared"[Text Word] OR "groups"[Text Word] OR "case control"[Text Word] OR "multivariate"[Text Word]). Search strategies were modified to meet the requirements of each database in combination with database-specific filters for observational studies, where these were available, detailed search strategies for each database are summarized in the **Supplementary Material 2**. There were no language restrictions. All searches were performed by trained investigators (NBO and CHCG) for studies published between 1981 and April 2023.

Study eligibility criteria

We included primary studies to obtain original information from observational studies involving patients diagnosed with OMMP, including cohort studies, cross-sectional studies, case-control studies, and case series. Articles non available in full text, case series including less than 10 eyes or patients, case reports, and systematic reviews were excluded.

Patient inclusion and exclusion criteria

Inclusion criteria were 1) patients with diagnosis of OMMP only or concomitant involvement of other mucous membranes, with any degree of inflammation, based on the definition of OCP by Mondino and Brown in 1981 (15), and the actualizations on the first international consensus about MMP in 2002 (5) and the clinical definition of the European guideline for the diagnosis and management of MMP in 2021 (4), also those with detection of autoantibodies against the basement membrane zone on DIF, and 2) patients of all ages, sexes, races, and ethnicities wherever reported. Exclusion criteria were: patients with concomitant diagnosis of cicatricial conjunctivitis of other etiologies, such as Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, linear IgA bullous dermatosis, acquired epidermolysis bullosa, drug-induced cicatrizing conjunctivitis, graft-versus-host disease, mucocutaneous paraneoplastic syndromes, atopic keratoconjunctivitis, ocular rosacea, and ocular surface squamous neoplasia.

Study selection

At first, all search results were downloaded in RIS format and organized through the Zotero® reference manager, creating an exhaustive database of identified articles. This was followed by removing duplicate articles using the duplicate finding function of Zotero® and then a secondary check was performed using Rayyan® research collaboration platform. Non-duplicate articles were randomly assigned and independently screened by three pairs of reviewers (NBO-DPP, MVOH-MJRO, SRS-DPT) by title and abstract, all trained in the clinical definition and diagnostic criteria of OMMP, through the Rayyan® research tool. Then, potentially eligible articles were screened in full text according to predefined eligibility criteria. As a result of this review process, the articles were categorized as "included", "excluded" or "in doubt", and documented in a Microsoft Excel® database. Study selection was performed in a standardized and independent process. Articles published in languages other than English were translated using DeepL translator®. Any discrepancies in eligibility were resolved by consensus among the authors and if not resolved, a specialist in the field was consulted ADLT. The selection process can be found in **Figure 1**.

Data extraction

Data were collected by six reviewers independently (NBO, DPP, MVOH, MJRO, SRS, DPT) and validated by two of them (NBO-MJRO). The extraction of the information was carried out systematically in a Microsoft Excel® spreadsheet. Studies reporting continuous variables such as means, standard deviation (SD), median, and range were extracted as such. The following information was collected: 1) general study characteristics: first author, publication year, DOI, geographic location of the study, study design, sample size; 2) study population characteristics: age, sex, and race; 3) general characteristics of OMMP: unilateral or bilateral involvement, time to diagnosis, severity stage at diagnosis, IFD positivity and extraocular involvement; 4)

ocular signs, symptoms, and complications: visual acuity, conjunctival inflammation, eyelid and/or eyelash involvement, ocular surface keratinization, other ocular surface signs, Schimer's test. The time to diagnosis was described in the articles as the time from symptoms onset until the diagnosis is established. To unify how this variable was reported, those data reported in terms of days or years were transformed into months, and those reported in months were extracted in the same way. Also, the best-corrected visual acuity (BCVA) reported based on the Snellen chart was transformed into logMAR according to the Visual Acuity Conversion Chart published in the Journal of Cataract & Refractive Surgery (16).

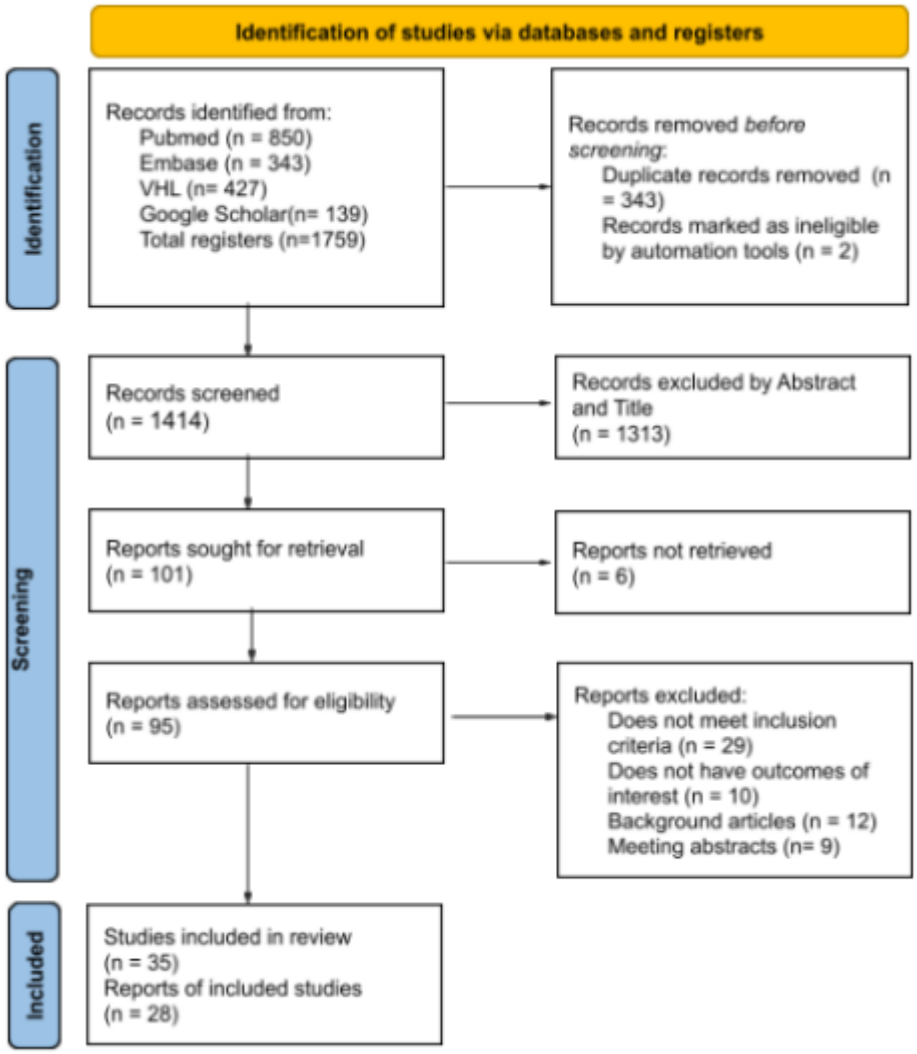


Fig 1. PRISMA flow diagram for selected studies included in the systematic review and meta-analysis (13)**.**

Risk of bias assessment

To assess the risk of bias, validated tools were used based on the study design of each article. For Case-control studies, we used the tool contributed by the Clinical Advances Through

Research and Information Translation (CLARITY) group at McMaster University (17). This scale evaluates 1) assessment of exposure, 2) ascertainment of exposure, 3) selection of cases, 4) selection of controls, 5) comparability and analysis of the data. Cohort studies were also assessed with the CLARITY tools to assess risk of bias (18). This scale consists of the following items: 1) selection of exposed and non-exposed cohorts, 2) assessment of exposure, 3) outcome of interest was not present at the start of the study, 4) exposed and unexposed matching, 5) prognostic factors, 6) assessment of outcome, 7) follow up, and 8) co-interventions. For Cross-sectional studies, the Hoy, et al. (19) modified tool was used. This tool evaluates 1) the study's target population, 2) the sampling frame representation, 3) the selection of the sample, 4) the likelihood of non-response bias, 5) the data collection source, 6) the case definition, 7) the instrument that measured the parameter of interest, 8) data collection consistency, 9) follow up period and 10) appropriate numerator(s) and denominator(s) for the parameter of interest. These items comprise four domains: selection, nonresponse, measurement, and analysis bias, and include a summary risk of bias assessment: bias due to external validity and bias due to internal validity. Finally, for Case series studies we used the Hassan Murad 'Methodological quality and synthesis of case series and case reports' assessment scale (20), consisting of 1) population selection, 2) ascertainment of exposure or outcome, 3) causality, and 4) sufficient reporting details.

The risk of bias was assessed following the recommendations of each tool, nevertheless, we condense the scoring as follows: for case-control and cohort studies, in the questions answered as 'definitely yes', we assigned a 'low risk of bias', for 'probably yes' or 'probably no' we designated the term 'some concerns' and for 'definitely no' answers we attributed a 'high risk of bias' (**Figure 2 and 3**). In cross-sectional studies, each "yes" counted as one point, the external validity was estimated as High for scores 0-1, denominated as Some Concerns for score 2, and designated as Low for score 3+, likewise, internal validity was labeled as High for scores 0-2, considered as Some Concerns for score 3, and classified as Low for scores 4+ (**Figure 4**). Lastly, in case of series studies, if the answer was 'yes' we designated a 'low risk or bias', if the answer to the question was 'no' we categorized it as a ´high risk of bias' and if the question was not applicable we labeled as 'some concerns' (**Figure 5**). Studies were considered graded as high risk of bias if any domains (internal or external validity) or questions for CLARITY or Hassan Murad tool were rated as a high risk of bias. The figures were designed using Robvis, a visualization tool (21).

Data synthesis and statistical analysis

For the qualitative analysis, we made a narrative description containing the characteristics of the included studies along with the extracted data relevant to the results of this review, related to the frequency of clinical manifestations and complications of OMMP, and presented them through summary tables, subdivided by general characteristics, and ocular manifestations and complications, regardless they were included or not in the meta-analysis.

Statistical analyses were conducted using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria) using the R Package (dmetar version 0.0.9000) (22). Meta-analyses of proportions were performed with a 95% confidence interval (CI) to construct forest plots for categorical data. The statistical heterogeneity of each study was assessed using the chi-square test and I2 statistics. The weighting of articles was performed using the generic inverse variance method to analyze primary outcomes reported as proportions using a fixed-effects model if heterogeneity was low (I2 <50%), and a random-effects model was employed if heterogeneity was significant (I2 >50%). To evaluate publication bias in Meta-analysis with more than eight studies we performed a Fail-Safe N analysis, rank correlation test, and asymmetry test. Besides, we carried out subgroup analyses based on the geographic location of the study. Additionally, pooled analysis was conducted for some continuous measures (mean age with standard deviation, and average time to diagnosis), as we did not have comparators. Results were considered statistically significant if P <0.05.

RESULTS:

Study selection

A total of 1,759 studies were initially identified as potentially relevant studies. Of these, 343 duplicates were removed, and 2 records were retracted manuscripts. Posteriorly, one thousand three hundred thirty-three articles were excluded in the initial screening by title and abstract, and 101 studies were included for full-text review. Nonetheless, six articles could not be retrieved. Finally, 95 articles were evaluated and included in the full-text review, of which 29 did not meet inclusion criteria, 10 did not have outcomes of interest, 12 were background articles and 9 were meeting abstracts so they were discarded (Causes of exclusion by article are described **Supplementary Material 3)**. In the end, 35 studies were included for qualitative review, comprising 1,439 patients and 1,040 eyes, and 28 studies for meta-analysis. The main characteristics of the included studies are summarized in **Table 1**. More detailed information is shown in **Figure 1**.

Study characteristics

Out of the 35 analyzed studies, 24 were cohort studies, of which 12 presented a low risk of bias (23–34), 11 raised some concerns (35–45) due to the evaluated of exposed and unexposed matching, prognostic factors and assessment of outcome as some concerns in at least one category, and only 1 article presented a high risk of bias in the outcomes of interest (46) due to the selection of exposed and non-exposed cohorts graded as high risk (**Figure 3**). Besides, 8 were cross-sectional studies, with six scoring a high risk of bias (47–52) due to external validity and the other two scoring a low risk of bias (7,53) (**Figure 4**). As for case-control studies, 2 studies were identified, one presenting a high risk of bias (54) related to high risk in the ascertainment of exposure, selection of controls, and comparability and analysis of the data,

and the other one presenting a low risk of bias (55) during the evaluation (**Figure 2**). Finally, 1 case series was analyzed and scored with a high risk of bias (56) due to causality graded as high risk of bias (**Figure 5**).

In the qualitative analysis, the summary of the data extracted from the 35 studies included, regarding the clinical characteristics of the patients with OMMP are described in **Table 2**. For the quantitative analysis, 28 studies were included, 19 cohort studies, 8 cross-sectional studies, and one case-control study. Of these 28 articles included in the meta-analysis, 19 were carried out in North America, 5 in Europe, 3 in Asia, and one in South America.

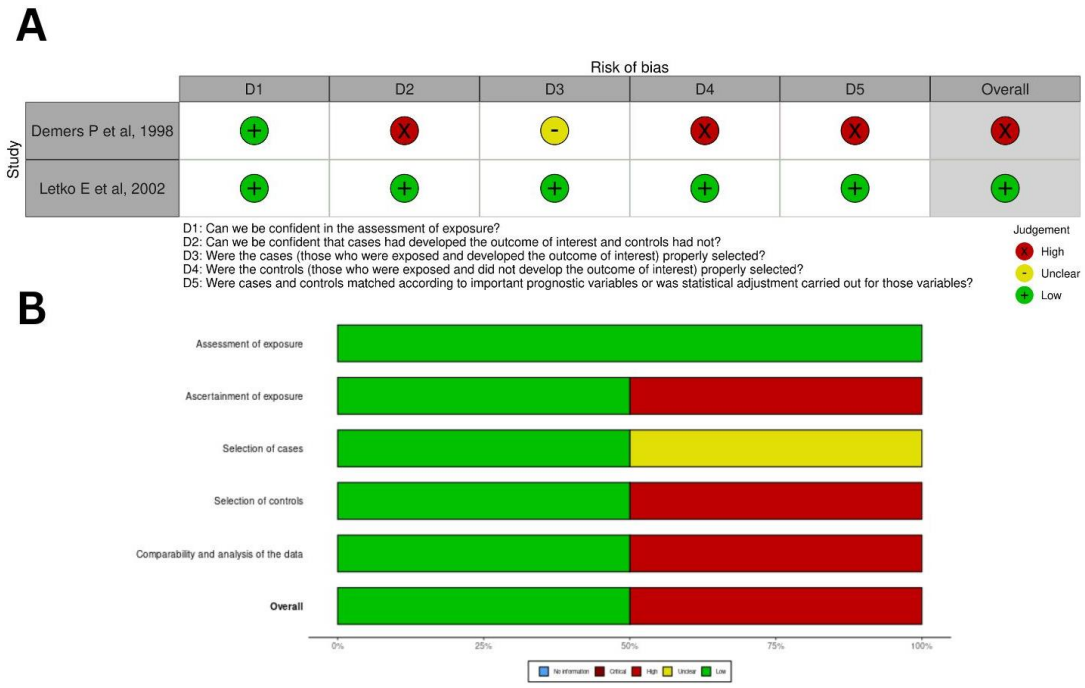


Fig 2. Risk of bias summary across case-control studies using CLARITY tool for case-control studies (17) **.** (A). CLARITY tool for case-control studies traffic light summary; (B). Risk of bias summary plot across case-control studies.

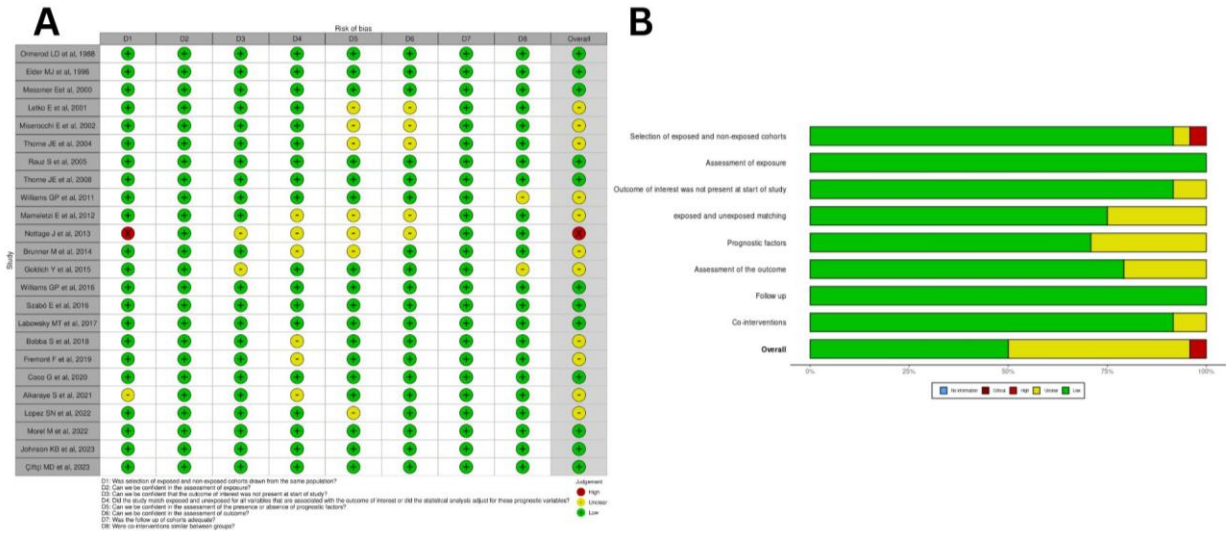


Fig 3. Summary across CLARITY tool for cohort studies (18)**.** (A). CLARITY tool for cohort studies traffic light summary; (B). Risk of bias summary plot through control studies.

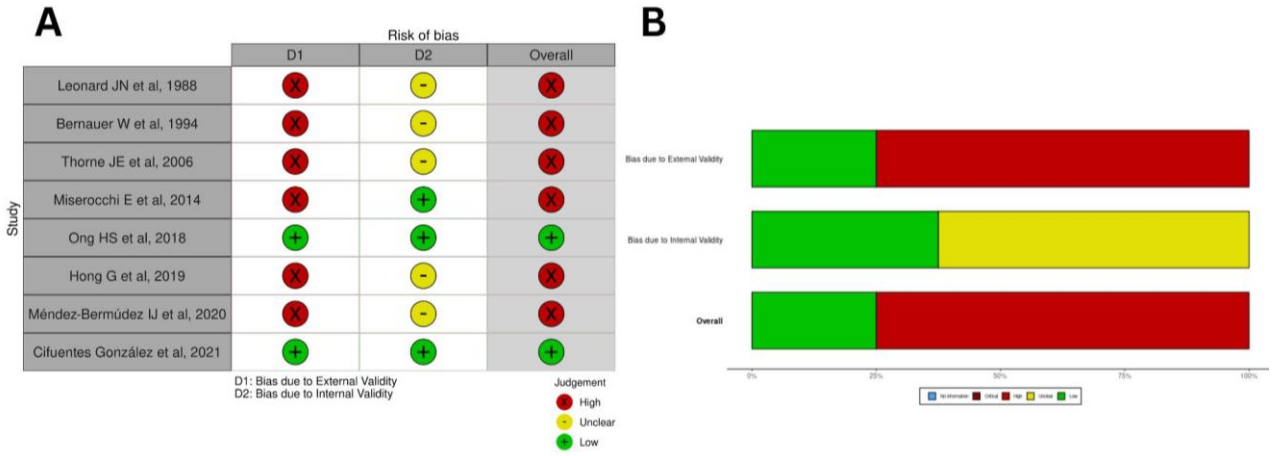


Fig 4. Summary of cross-sectional studies risk of bias using Hoy, et al. modified tool (19)**.** (A). Traffic light summary for cross-sectional studies using Hoy, et al modified tool; (B). Risk of bias summary plot through cross-sectional studies.

Fig 5. Traffic light for case series study using Hassan Murad 'Methodological quality and synthesis of case series and case reports' assessment scale summary (20)**.**

Baseline features of OMMP

Among 20 studies that reported the average age at diagnosis in 752 patients, the mean age was 68.2 (SD 4.30) [Range 60.4-75] years old (23–25,29,31,32,34,36,39–41,43–45,47,50,51,54–56). Furthermore, in 5 studies comprising 262 patients that reported the average time to diagnosis, the mean time was 55.1 (SD 13.2) [Range 35.4-71] months (29,41,42,47,56). Regarding the prevalence of OMMP was between 0.22 per million inhabitants and 25 per 1,000 patients (7,32), and the incidence reported was 0.24 per million inhabitants to 11 per 10,000 patients (7,32,42) as shown in **Table 2**. Nevertheless, this information could not be evaluated in meta-analysis given the data heterogeneity.

Visual acuity at diagnosis of OMMP

Multiple studies described the visual acuity (VA) at the time of diagnosis. Most authors found that the most frequent BCVA was LogMAR less than 0.30 up to 91%, being more common in the United Kingdom, followed by the United States (24,28,36,38,43,56). Except for two articles that retrieved a BCVA with a LogMAR $\geq$ 1.00 as the most frequent in up to 77.7% of cases, one from Saudi Arabia and the other one from Turkey (34,44). The median BCVA most reported was LogMAR 0.40 with a minimum of -0.10 and maximum $\geq$3.00 (37,46) as illustrated in **Table 2.** Meta-analysis for this variable was not possible due to the heterogeneity of the data, since it was sometimes reported in terms of eyes and sometimes in terms of a number of patients.

Ocular manifestations and complications

The three more common ocular manifestations were trichiasis up to 92%, followed by entropion also up to 92%, and symblepharon in 83% of cases (23–25,27,29,31,32,37,39,39–42,51,52). Moreover, among other ocular symptoms/signs and complications, 17% to 28% were reported to have limbitis (24,42), ankyloblepharon between 4.6% and 28% (25,41,42), and punctate keratitis was present in 11.1% to 46% of cases (27,32,36,42). Positivity of Schirmer's test was reported only in two studies, ranging from 22.7% to 27.6% (27,49). Furthermore, keratinization of the ocular surface can occasionally induce infectious keratitis, which occurred in 1.6% to 10% of the 3 studies reporting this event (23,36,42).

Conjunctival cicatrization may also result in corneal scarring leading to persistent epithelial defects ranging from 6% to 61.5% (23–25,27,32,34,36,39,42), and corneal opacities or neovascularization which range from 11% to 34% (31,39,42).

In two studies that reported the grade of inflammation at diagnosis, moderate to severe conjunctival inflammation was least frequent accounting for 22% of cases (26,42), leaving a 77.7% with a mild conjunctival inflammation (26).

Finally, Thorne, et al calculated the incidence rate for OMMP among patients with only extraocular MMP, over the first 5 years was 0.05 per person-year and for 10 years was 0.04 per person-year (37). Another study published in the United States reported the incidence rate for ocular disease in patients who had only extraocular involvement, which was 0.014 per person-year (95% CI 0.005/PY; 0.034/PY) over 22 years of follow-up (51).

Classification of OMMP at diagnosis

For OMMP classification, different clinical disease scoring systems have been described for objective assessment of disease severity, therapy outcomes, and longitudinal disease follow-up. Foster's Classification System was the most widely used among the included studies, with stage III being the most frequent at the time of diagnosis, ranging from 35% to 100% (24,25,27,30,36,40,41,44,46,52,56). However, in the study by Miserocchi et al, presenting stage III was an inclusion criteria (50). Stage II was the second most frequently reported, ranging between 4.1% to 34% (24,27,30,36,40,41,46,56), followed by stage I presented between 0% in up to 27.7% (24,25,27,30,40,41,44,46,56). Finally, stage IV was the least frequently reported, ranging from 0% to 40% (24,25,27,30,38,40,41,44,46,56), as shown in **Table 2**.

Subsequently, Mondino and Brown Classification System were the second one most reported, in which stage I was present in 3.7% in up to 38.8%, stage II ranged from 19.6% to 30.5%, stage III accounted for 17% to 34% of cases and stage IV was present in up to 42.4% (24,40,42).

Lastly, the Tauber Classification System was the least frequently reported, being stage IIb accounting for the largest share with 29% of eyes in one of the two studies, followed by stages IIa and IIIb with 21% of eyes each (43). Çiftçi MD et al, reported that stage IV was the most frequent stage representing 31.8% of eyes, followed by stages IId and IIId with 18.1% of eyes each (34).

Meta-analysis

Frequency of OMMP by gender. In the meta-analysis for the frequency of OMMP in females, 1,345 patients were included (**Figure 6**), and the overall proportion of affected females was 56% (95% CI 53%; 59% I2 = 49%; fixed-effects, Fig 6) ($P < 0.01$). Subgroup analysis shows that the continent with the highest proportion of females with OMMP was Asia with 63% (95% CI 49%; 75%, I2 = 0%; ($P = 0.37$); fixed-effects), followed by Europe with 58% (95 CI 49%; 65%, I2 = 30%; ($P = 0.22$); fixed-effects), and North America with 56% (95% CI 51%; 61%, I2 = 57%; ($P < 0.01$); random-effects) (7,23–34,36–38,41,43–45,47–51,53,54,56). The funnel plot of all studies evidences a Fail-Safe N analysis (Fail-Safe N = 17900; P <0.0001), Rank correlation test (Tau = 0.0133; P = 0.9213), Asymmetry (Z= -0.4992, P= 0.6176) (**Supplementary Material 4**).

Regarding the frequency of OMMP in males, one thousand three hundred forty-five patients were analyzed and it was 44% (95% CI 40%; 49%, I2 = 61%; random-effects, **Figure 7**) (*P* < 0.01). Due to the high level of heterogeneity, an analysis by continental subgroups was conducted, where the p-value lost statistical significance (*P* = 0.61; random effects). The highest proportion was reported in North America with 45% (95% CI 39%; 50%, I2 = 68%; (*P* <0.01); random-effects), followed by Europe with 42% (95% CI 35%; 51%, I2 = 30%; (*P* = 0.22); fixed-effects) and Asia with 39% (95% CI 26%; 53%, I2 = 44%; (*P* = 0.17); fixed-effects) (7,23–34,36–38,41,43–45,47–51,53,54,56). The funnel plot of all studies showed a Fail-Safe N analysis (Fail-safe N = 10551, P <0.0001), Rank correlation test (Tau = 0.0080, P= 0.9527), Asymmetry (Z= 0.3534, P = 0.7238), and can be consulted in **Supplementary Material 4**.

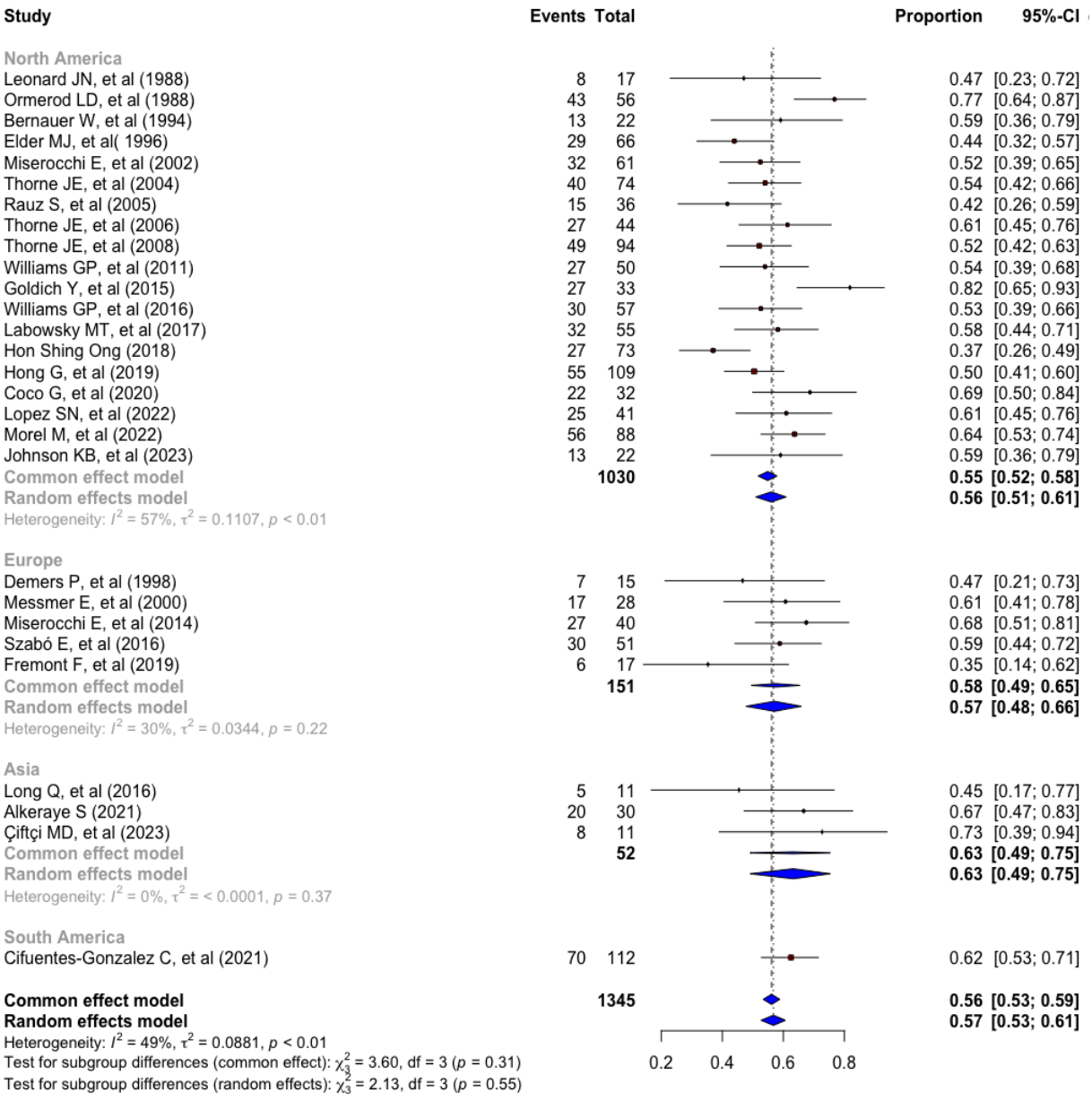


Fig 6. Frequency of OMMP in females segmented by continent.

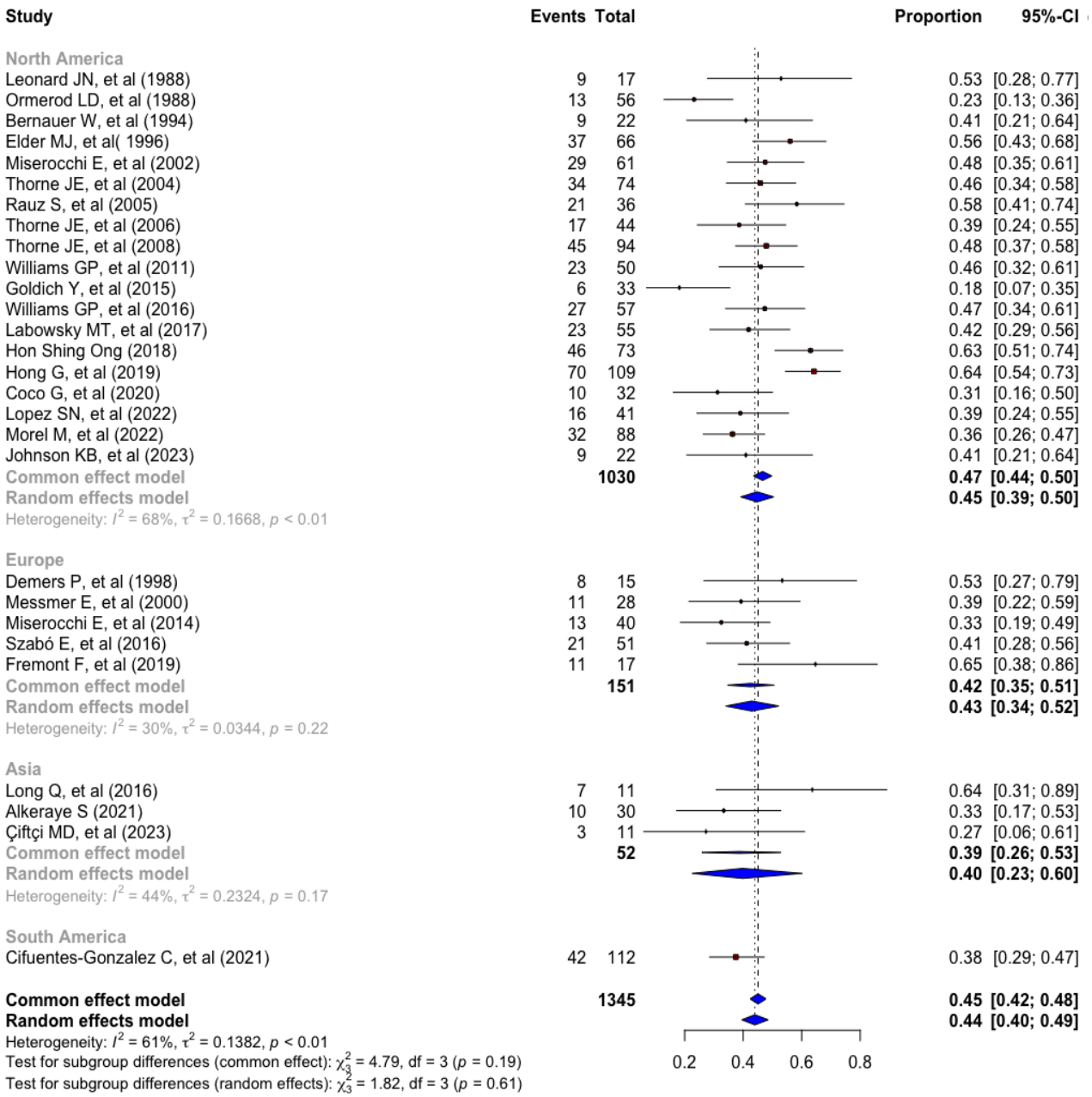


Fig 7. Frequency of OMMP in males segmented by continent.

Frequency of OMMP by race. 13 studies including 777 patients were analyzed to assess the overall frequency of OMMP in Caucasians, and it was 88% (95% CI 85%; 90%, I2 = 19%; fixed-effects, **Figure 8A**) (*P* = 0.25) (26–28,30,32,33,36,37,45,46,49,51,53). The funnel plot of all studies showed a Fail-Safe N analysis (Fail-safe N = 45423; P <0.0001), Rank correlation test (Tau = -0.3590; P= 0.1000), Asymmetry (Z= -3.914; P <0.0001) (**Supplementary Material 4**). In the African descent population the overall proportion estimated in 511 patients included in 8 studies, was 6% (95% CI 4%-9%, I2 = 0%; fixed-effects, **Figure 8B**) (*P* = 0.55) (27,28,30,32,45,46,49,51). As for other races, 9 studies comprising 564 patients were explored

and the global proportion of OMMP in this group was 7% (95% CI 5%; 10%, I2 = 49%; fixed-effects, **Figure 8C**) (*P* = 0.05) (26,28,30,32,36,45,49,51,53). The funnel plot of all studies evidenced a Fail-Safe N analysis (Fail-safe N = 95; P= <0.0001), Rank correlation test (Tau = 0.5000; P = 0.0752), Asymmetry (Z = 3.5596, P= 0.0004) (**Supplementary Material 4**)

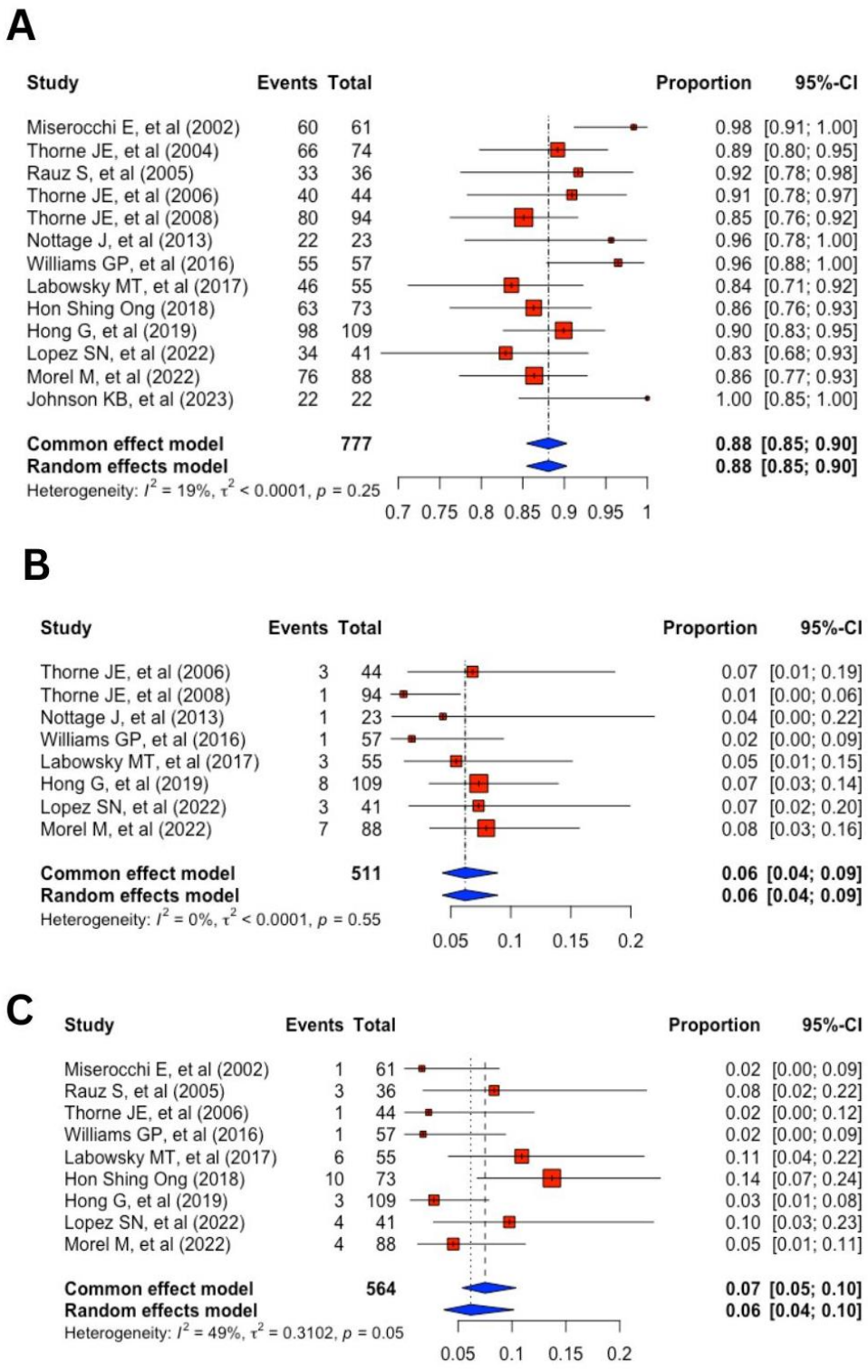


Fig 8. Frequency of OMMP by race. (A). Caucasians, (B). African descents, (C). Others.

Laterality of OMMP at diagnosis. Six studies outlined the frequency of ocular involvement in terms of laterality at diagnosis (27,34,39,41,43,46). The overall proportion of bilateral ocular compromise was 90% (95% CI 78%; 96%, I2 = 59%, random-effects; **Figure 9B**) (*P* = 0.03) (27,34,39,41,43,46). A subgroup analysis by continent was performed given the heterogeneity, with a loss of statistical significance (*P* = 0.41; random-effects). North America demonstrated the highest proportion with 93% (95% CI 87%; 96%, fixed-effects, I2 = 0%; (*P* = 0.57)) (27,41,46), and in Europe the overall proportion reported was 79% (95% CI 39%; 96%, random-effects, I2 = 62%; (*P* = 0.10)) (39,43).

On the other hand, the summarized effect size of four articles that reported unilateral ocular involvement at the time of diagnosis was 9% (95% CI 2%; 29%, random effects, I2 = 80%; **Figure 9A**) (*P* <0.01) (27,39,41,43). Due to the high heterogeneity, a subgroup analysis was carried out, where the p-value lost statistical significance (*P* = 0.06; random-effects). Unilateral ocular compromise was less frequent in North America with an overall proportion of 4% (95% CI 1%; 9%, fixed-effects, I2 = 12%; (*P* = 0.29)) (27,41), followed by Europe in which was 21% (95% CI 4%; 61%, random-effects, I2 = 62%; (*P* = 0.10)) (39,43).

DIF and IIF positivity for OMMP diagnosis. DIF on biopsy is supportive in the diagnosis of OMMP, its positivity in conjunctival biopsies was reported in 22 studies involving 624 patients, with a global frequency of 54% (95% CI 43%; 64%, random-effects, I2 = 81%, **Figure 10A**) (*P* <0.01) (24,28–33,37,38,40–48,54,56). The funnel plot of all studies evidences a Fail-Safe N analysis (Fails-safe N = 6498; P<0.0001), Rank correlation test (Tau = -0.1474; P = 0.3859), Asymmetry (Z= -0.5338; P= 0.5935) can be found in **Supplementary Material 4**. Additionally, DIF positive in oral biopsies for the diagnosis of OMMP was reported in only 3 studies studies, with an overall frequency of 31% (95% IC 8%; 69%, random-effects, I2 = 91%; **Figure 10B**) (*P* <0.01) (36,45,46).

Regarding IIF positivity for diagnosis of OMMP, in four studies including 114 patients reported that the overall proportion was 33% (95% CI 25%; 42%, fixed-effects, I2 = 2%; **Figure 10C**) (*P* = 0.79) (37,38,47,56).

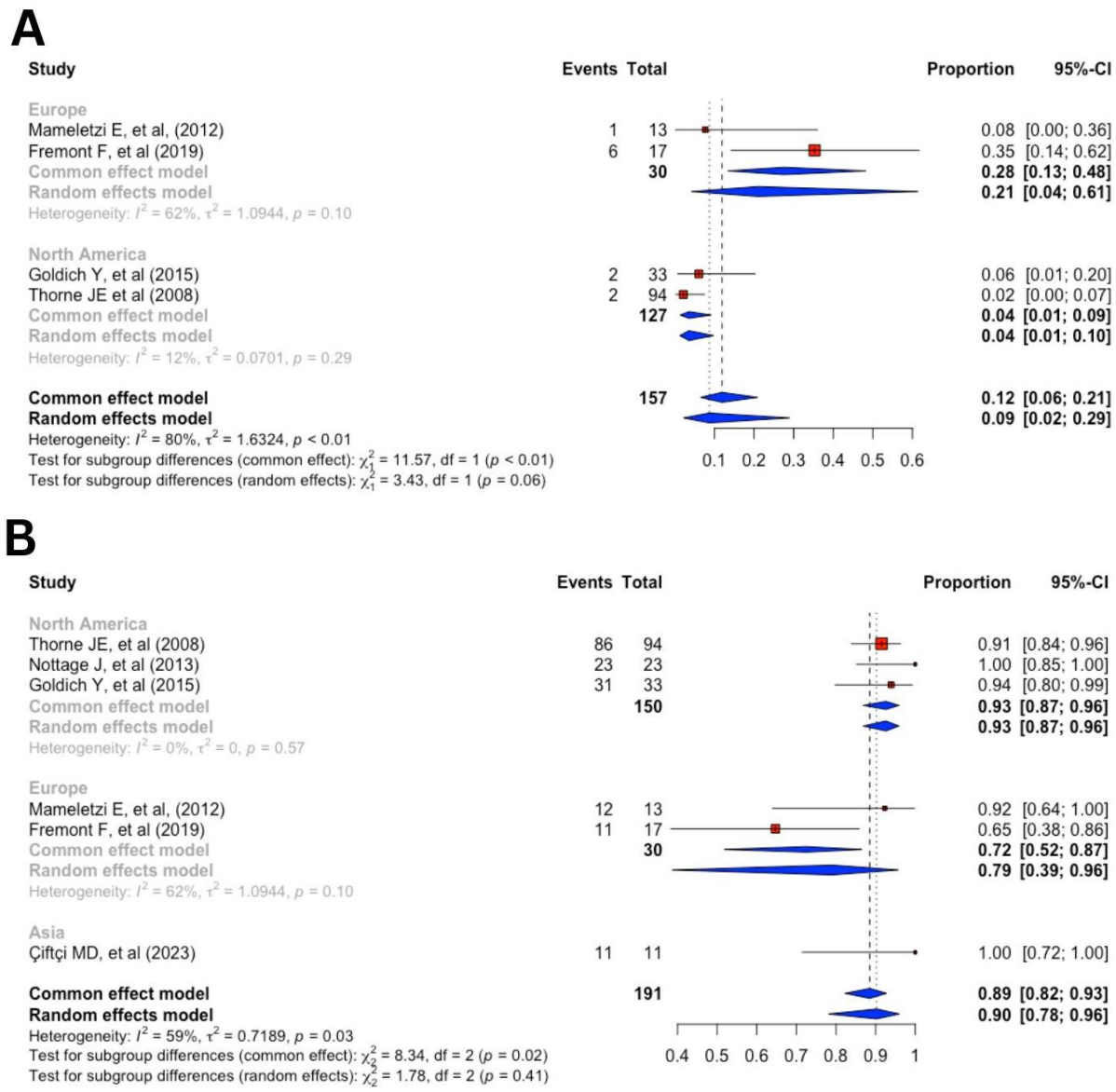


Fig 9. Laterality of OMMP at diagnosis. (A). Unilateral, (B). Bilateral.

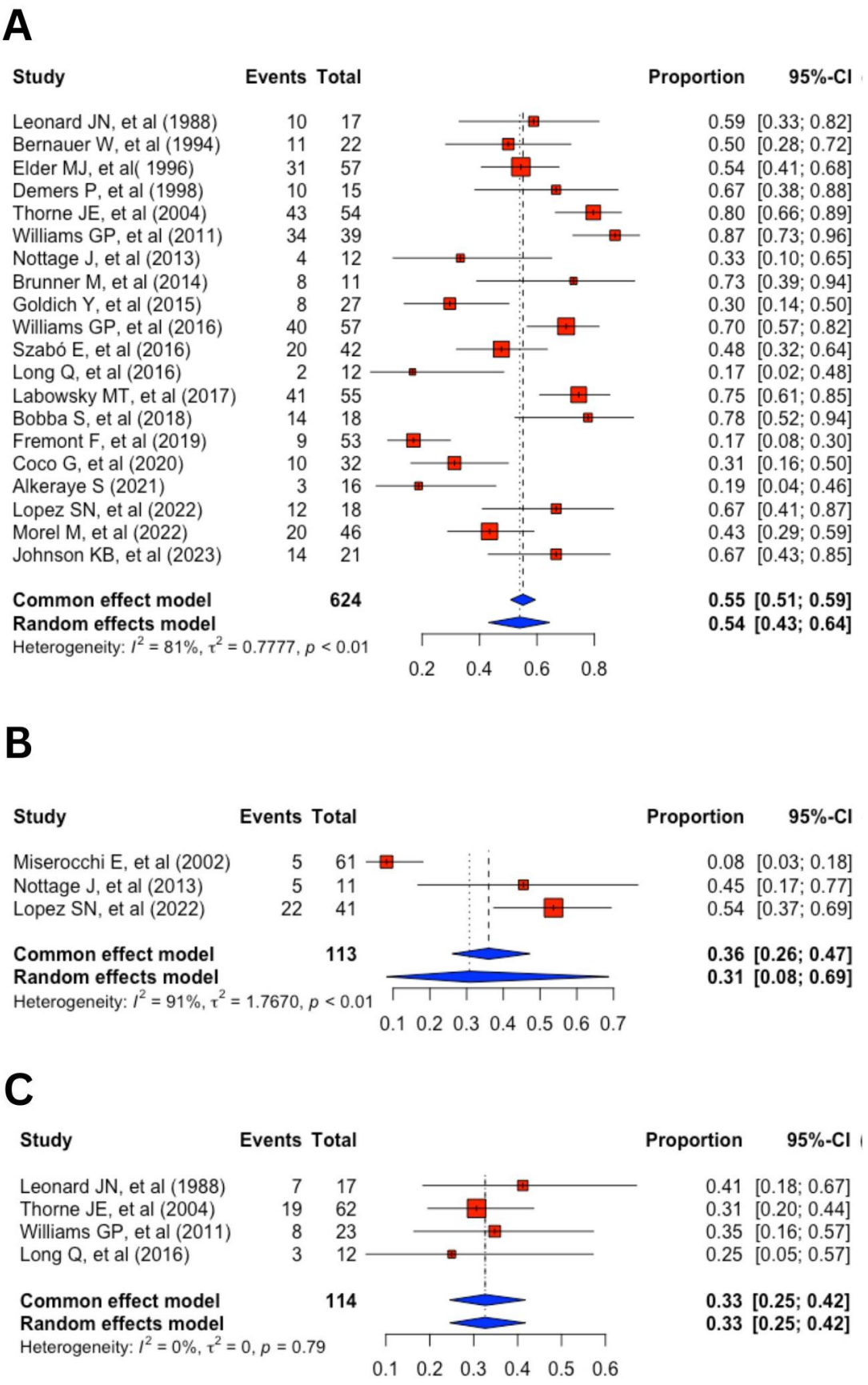
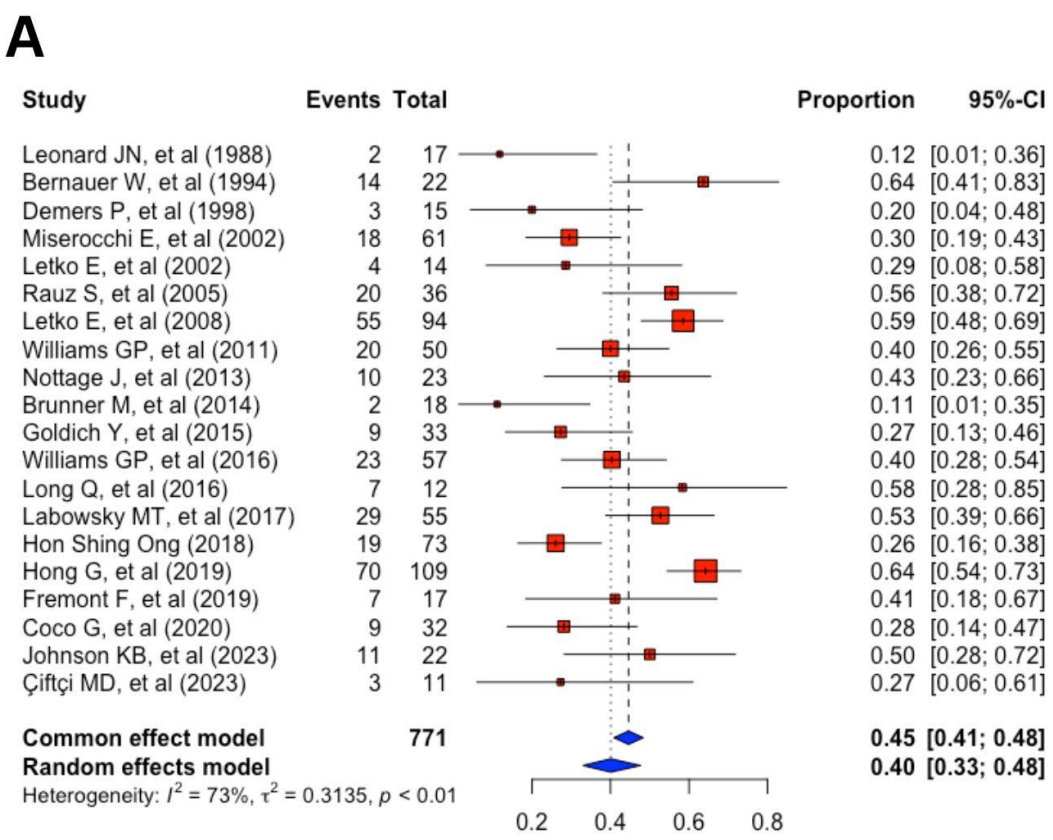


Fig 10. DIF and IIF positive for OMMP diagnosis. (A). Conjunctival biopsy DIF, (B). Oral biopsy DIF, (C). IIF positivity.

Extraocular involvement in patients with OMMP. Patients with OMMP can present with ocular disease alone or simultaneously with extraocular manifestations, the overall frequency of oral involvement was 40% (95% CI 33%; 48%, random-effects, I2 = 73%; **Figure 11A**) (*P* <0.01) among 20 studies including 771 patients (26–28,30,31,33,34,36,38,40,41,43,46–48,51,53–56). A funnel plot of all studies can be found in supplementary material, the Fail-Safe N analysis (Fail-safe N = 3765; P <0.0001), Rank correlation test (Tau = 0.0000; P = 1.000), Asymmetry (Z = -0.1856; P= 0.8527) (**Supplementary Material 4**). Skin involvement in 14 studies enrolling 617 patients was estimated to have an overall frequency of 18% (95% CI 14%; 24%, random-effects, I2 = 55%, **Figure 11B**) (*P* <0.01) (26–28,30,31,33,34,36,38,40,41,43,48,51). The funnel plot of all studies showed a Fail-Safe N analysis (Fail-safe N = 618; <0.0001), Rank correlation test (Tau = 0.1648; P= 0.4506), Asymmetry (Z= 0.5921; P= 0.5538), as shown in **Supplementary Material 4**.

Moreover, for pharynx involvement the overall frequency was 18% (95% CI 12%; 25%, fixed-effects, I2= 32%, **Figure 11C**) (*P* = 0.21) (26,40,43,53,55), larynx involvement was reported in 6% (95% CI 1%; 29%, random-effects, I2= 77%, Fig 11D) (*P*= 0.01) (27,36,37,55). Lastly, genital compromise overall frequency was 8% (95% CI 4%; 19%, fixed-effects, I2= 0%; **Figure 11E**) (*P* = 0.38) (26,48,55).



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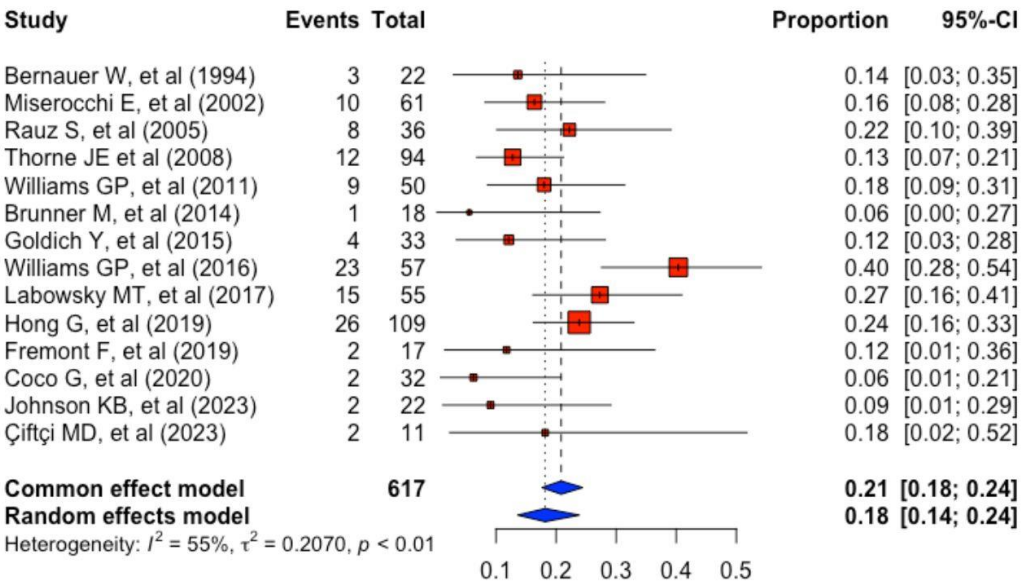

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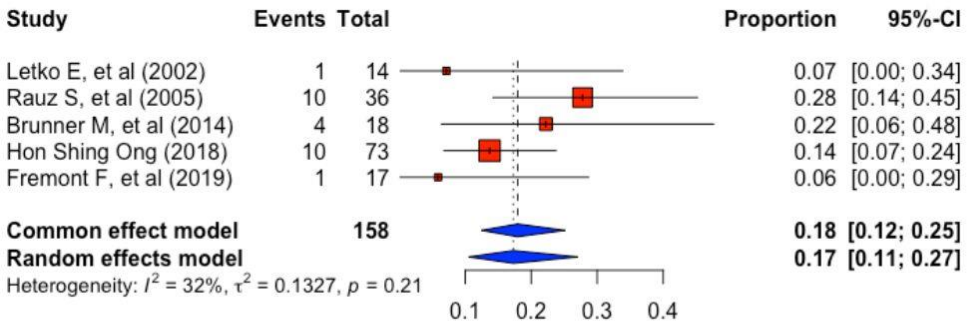

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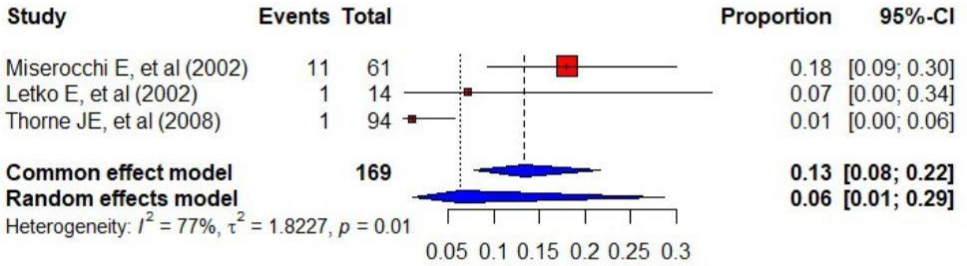

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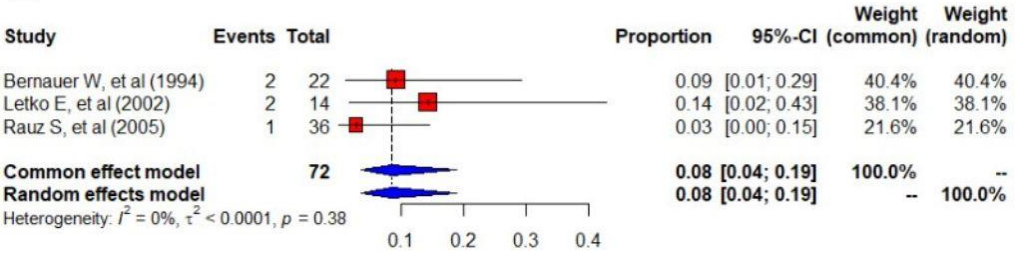

Fig 11. Extraocular involvement. (A). Oral, (B). Skin, (C). Pharynx, (D) Larynx, (E). Genital.

DISCUSSION

Our systematic review and meta-analysis identified 35 studies investigating epidemiological data, ocular manifestations, and complications, as well as extraocular involvement, and some tools that support diagnosis. Based on the available evidence, our study found that OMMP prevalence ranges from 0.22 per million inhabitants to 25 per 1,000 patients (7,32), and the overall incidence was between 0.24 per million inhabitants to 11 per 10,000 patients (7,32,42). This is significantly higher than the incidence reported in some studies published before 1986, which varied from 1 per 12,000 to 1 per 60,000 patients (57).

OMMP is a condition that predominantly affects older people, especially nearing the seventh decade of life, as evidenced in our study estimating an average of 68.2 years old at diagnosis (23–25,29,31,32,34,36,39–41,43–45,47,50,51,54–56). Females represented the majority of the affected population, contributing to 56% of the overall population considered in our study, with a subgroup analysis showing that the highest proportion was located in Asia up to 63%, followed by Europe and North America (7,23–34,36–38,41,43–45,47–51,53,54,56). However, the meta-analyses of OMMP frequency by race evidenced that the summarized effect was considerably higher in Caucasians (26–28,30,32,33,36,37,45,46,49,51,53) compared to African descents and other races, which may contradict a long-established misconception that OMMP has no racial predilection (6,58). Nevertheless, since few studies reported on this variable conclusions about race predilection are not reliable enough. Also, it should be considered that the meta-analysis of Caucasians and other races frequencies has a high risk of publication bias, which is why it should be analyzed carefully.

Mameletzi et al described that patients initially complained of redness, tearing, burning, decreased vision, and foreign body sensation (39), which can often delay diagnosis because of the unspecificity of the clinical presentation at initial stages. We observed that the mean time elapsed from symptom onset to diagnosis was 55.1 months, supporting this argument (29,41,42,47,56). Even though the diagnosis is mainly clinical, DIF in conjunctival biopsy can support the diagnosis, in our study, the overall frequency shows that at least half of the patients have a positive conjunctival DIF, which continues to support the fact that the diagnosis remains primarily clinical. Surprisingly, we found that positive DIF in oral biopsies for OMMP diagnosis was frequent, with an overall proportion of 31%. Even though few data have been reported, we suggest further studies on this variable, which can also support timely diagnosis.

OMMP is characterized by chronic conjunctivitis leading to multiple complications, usually bilateral as reported in our meta-analysis, reported up to 90% (27,34,39,41,43,46). It can commonly compromise eyelids and/or eyelashes; in our study we found trichiasis to be the most common complication reported overall, closely followed by entropion and symblepharon (23–25,27,29,31,32,37,39–42,51,52). Although dry eye syndrome has been described as a frequent complication of OMMP, in our study only up to 27.6% presented a positive Schirmer's test (27,49). As the disease follows its natural course, more severe complications were increasingly described, such as limbitis, ankyloblepharon, and punctate keratitis

(24,25,27,32,36,41,42), evidencing how the continuous formation of scar tissue resulting from chronic conjunctivitis results in notorious disruption of the normal ocular surface structure and functionality.

Although, outcomes such as corneal scarring, opacities, and/or neovascularization, as well as persistent epithelial defects, were less frequently reported, and ended up contributing to an unfavorable visual prognosis (23–25,27,32,34,36,39,42). Chronic changes resulting in conjunctival scarring may also lead to the development of infectious complications, although in our study the proportion of cases was low, it may be a complication that occurs repeatedly. Ormerod D, et al reported over 11 years, 33 episodes of infectious keratitis in 28 patients (23).

Regarding visual acuity (VA) at the time of diagnosis, multiple studies reported that the most frequent BCVA was LogMAR less than 0.30 (24,28,36,38,43,56). However, some authors reported it in terms of eyes, whereas others reported it in terms of the number of patients, accounting for a high data heterogeneity, which makes it difficult to make reliable conclusions. What is indisputable, is that OMMP progressively leads to a severe visual impairment that ultimately disturbs the patient's quality of life and can end in blindness if not properly managed.

After assessing all the scoring systems, we consider the Tauber Classification System to provide the most complete description of the stage of OMMP in which a patient is, at the time of evaluation. It is considerably more thorough than its counterparts, given that it evaluates all of the variables that are considered in Foster's Classification System, as well as Mondino and Brown's Classification System. Nonetheless, we take this opportunity to highlight the need for more studies comparing all three staging systems, so that an official agreement among practitioners can be reached to use a single one so that in the near future we all speak on the same terms.

Furthermore, extraocular involvement in patients with OMMP is quite frequent; we found that oral involvement predominated over other locations, followed by skin and pharyngeal involvement. The least affected sites were the larynx and genital area. Therefore, as clinicians, we have to consider that MPMO can present with multisystem involvement which can also lead to multiple extraocular complications. Some studies reported the risk of developing MPMO in patients with extraocular involvement only (37,51), however, more studies are needed to assess this rate, as well as a unified form of reporting.

As for the limitations of our study, some variables such as BCVA, ocular manifestations and complications, and disease classification, presented high data heterogeneity, sometimes reported in terms of eyes and sometimes in terms of patients, so it was not possible to perform a meta-analysis of these variables. In addition, BCVA was sometimes reported based on the Snellen chart, so it was necessary to convert the data to a more standardized form, in LogMAR, to be able to analyze the frequency of this variable. On the other hand, some of the meta-analyses performed showed a high degree of heterogeneity, so some data must not be overlooked when analyzing the results.

Finally, this is the first meta-analysis that provides detailed information on the ocular characteristics of OMMP. It is expected to be very useful for the medical community, especially for ophthalmologists and dermatologists who most often face this entity, as a reference to better understand the manifestations of the disease and establish timely diagnoses and treatment. Considering the evidence presented previously and the results of our meta-analysis, we suggest that patients around 60 years of age with symptoms suggestive of cicatricial conjunctivitis should be considered for a diagnosis of OMMP, especially in those with extraocular involvement, and can also be supported by the DIF result on conjunctival biopsy, even though further studies are needed. Lastly, it provides an opportunity to suggest a more unified and standardized way of reporting some variables, such as visual acuity, ocular manifestations, and the classification system of the disease.

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SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher's website.

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DATA AVAILABILITY STATEMENT

Additional data is available from the corresponding author on request.

ETHICS DECLARATIONS

Ethics approval and consent for participation and publication: not applicable.

AUTHOR CONTRIBUTIONS

Natalia Bocanegra Oyola (**NBO**) and Carlos Humberto Cifuentes González (**CHCG**) performed the search strategy. Pairs of review authors (**NBO**, Daniella Pardo Pizza (**DPP**), María Valentina Oliver Hernández (**MVOH**), María Juliana Romero Osorio (**MJRO**), Sofía Romero Santos (**SRS**), Daniela Parra Tanoux (**DPT**)) examined the articles based on inclusion criteria. All the authors resolved article selection conflicts by consensus. **NBO**, **DPP**, **MVOH**, **MJRO**, **SRS**, **DPT** were involved in data curation. Formal analysis was realized by **NBO**, **CHCG**, Ana María Barragán (**AMB**), and Alejandra de-la-Torre (**ADLT**). Original draft was written by **NBO** and **DPP**. **ADLT**, **CHCG**, **AMB** and **NBO**, reviewed the manuscript. Supervision was incharge of **AMB** and **ADLT**. All authors approved the final version submitted for publication.

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Table 1. Main characteristics of the included studies

Study	Country	Study Design	Study size	Age (Years)	Sex (% Females)	Time to diagnosis
Leonard JN et al, 1988 (47)	United States	Cross-sectional	Patients (n = 17)	M 66 (min 51 - max 80) years	47%	M 60 months SD (NR)
Ormerod LD et al, 1988 (23)	United States	Cohort	Patients (n = 56) Eyes (n = 69)	M 68 SD (± 12) years	77%	-
Bernauer W et al, 1994 (48)	United Kingdom	Cross-sectional	Patients (n = 22)	Me 74 (min 55 - max 87) years	59%	-
Elder MJ et al, 1996 (24)	United Kingdom	Cohort	Patients (n = 66) Eyes (n = 132)	M 67.1 SD (± 10.9) years	44%	-
Demers P et al, 1998 (54)	France	Case-control	Patients (n = 15)	M 73 (min 62 - max 87) years	47%	-
Messmer E et al, 2000 (25)	Germany	Cohort	Patients (n = 28)	M 73 (min 49 - max 89) years	61%	-
Letko E, et al, 2001 (35)	United States	Cohort	Patients (n= 6)	M 67.5 (min 50 - max 75) years	50%	-
Miserocchi E, et al, 2002 (36)	United States	Cohort	Patients (n= 61) Eyes (n= 122)	M 67 (min 38 - max 92) years	52%	-
Letko E, et al, 2002 (55)	United States	Case-control	Patients (n= 7) Eyes (n= 14)	M 65.4 (min 57 - max 80) years	57%	-
Thorne JE, et al, 2004 (37)	United States	Cohort	Patients (n= 74)	Me 67.4 (min 3 – max 90) years	54%	Me 9.5 months

Study	Country	Study Design	Study size	Age (Years)	Sex (% Females)	Time to diagnosis
Rauz S, et al, 2005 (26)	United States	Cohort	Patients (n= 36)	min 27 - max 85 years	42%	min 1 - max 144 months
Thorne JE, et al, 2006 (49)	United States	Cross-sectional	Patients (n=44)	Me 39 (min 20 - max 78) years	61%	Me 10 (min 0 - max 240) months
Thorne JE, et al, 2008 (27)	United States	Cohort	Patients (n=94) Eyes (n=188)	M 69 SD (38-91) years	52%	-
Williams GP, et al, 2011 (38)	United Kingdom	Cohort	Patients (n=50) Eyes (n=99)	M 67 SD (32-91) years	54%	Me 36 (min 0 - max 492) months
Mameletzi E, et al, 2012 (39)	Switzerland	Cohort	Patients (n=13)	M 68.3 (min 38 - max 88) years	-	-
Nottage J, et al, 2013 (46)	United States	Cohort	Patients (n=23) Eyes (n=46)	Me 67 (min 66.2 - max 81.5) years	52%	-
Miserocchi E, et al, 2014 (50)	Italy	Cross-sectional	Patients (n=40)	M 70.13 SD (± 11.48) years	68%	-
Brunner M, et al, 2014 (40)	Switzerland	Cohort	Patients (n = 18) Eyes (n = 36)	M 64 SD (± 13.2) years	-	-
Goldich Y, et al, 2015 (41)	Canada	Cohort	Patients (n = 33) Eyes (n = 64)	M 69.8 SD (± 11.9) years	82%	M 50.4 (min 0 - max 252) months
Williams GP, et al, 2016 (28)	United Kingdom	Cohort	Patients (n = 57) Eyes (n = 114)	M 72 SD (48-97) years	53%	Me 30 (min 1 - max 480) months

Study	Country	Study Design	Study size	Age (Years)	Sex (% Females)	Time to diagnosis
Szabó E, et al, 2016 (29)	Czech Republic	Cohort	Patients (n= 51)	M 60 years	59%	M 71 (min 29 - max 91) months
Long Q, et al, 2016 (56)	China	Case series	Patients (n= 12) Eyes (n = 24)	M 60.42 SD (± 10.39) years	45%	M 35.4 SD (± 34.2) months
Labowsky MT, et al, 2017 (30)	United States	Cohort	Patients (n= 55)	Me 62 years	58%	-
Bobba S et al, 2018 (42)	Australia	Cohort	Patients (n=18)	-	-	M 58.7 months
Ong HS et al, 2018 (53)	United Kingdom	Cross-sectional	Patients (n=73)	Me 60 (min 53-max 68) years	37%	Me 104 (min 54 - max 146) months
Hong G et al, 2019 (51)	United States	Cross-sectional	Patients (n=109)	M 66.9	51%	-
Fremont F et al, 2019 (43)	France	Cohort	Patients (n=17) Eyes (n=34)	M 75 SD (±11) years	35%	-
Mendez-Bermudez et al, 2020 (52)	Puerto Rico	Cross-sectional	Patients (n=8) Eyes (n=16)	Me 60.5 (36-66) years	62.5%	Me 8.5 (min 3 - max 24) months
Coco G et al, 2020 (31)	United Kingdom	Cohort	Patients (n = 32)	M 72 SD (± 12) years	69%	-
Alkeraye S et al, 2021 (44)	Saudi Arabia	Cohort	Patients (n = 30) Eyes (n = 60)	M 69.6 (min 42 - max 99) years	67%	-

Study	Country	Study Design	Study size	Age (Years)	Sex (% Females)	Time to diagnosis
Cifuentes-Gonzalez C et al, 2021 (7)	Colombia	Cross-sectional	Patients (n = 112)	-	63%	-
Lopez SN et al, 2022 (45)	United States	Cohort	Patients (n = 41)	Me 67 (min 43 - max 85) years	61%	-
Morel M et al, 2022 (32)	United States	Cohort	Patients (n = 88)	M 70.9 (min 44 - max 95) years	64%	-
Johnson KB et al, 2023 (33)	United States	Cohort	Patients (n = 22)	Me 73 (min 35 - max 98) years	59%	-
Çiftçi MD et al, 2023 (34)	Turkey	Cohort	Patients (n = 11) Eyes (n = 22)	M 76 (min 53 - max 87) years	73%	-

M: Mean, SD: Standard deviation, Me: Median, min: Minimum value, max: Maximum value, NR: Not reported

Table 2. Characteristics of OMMP

Study	Prevalence	Incidence	Visual acuity BCVA (LogMAR)	Ocular manifestations and complications	Classification	Extraocular involvement	Risk of OMMP
Leonard JN et al, 1988 (47)	-	-	-	-	-	Oral 11.7%	-
Ormerod LD et al, 1988 (23)	-	-	-	Trichiasis 52% Persistent epithelial defects 12% * Infectious keratitis 10%	-	-	-
Bernauer W et al, 1994 (48)	-	-	-	-	-	Oral 63.6% Skin 13.6% Genital 9%	-
Elder MJ et al, 1996 (24)	-	-	≥1.00 23.4% * ≥0.30 <1.00 13.6% * <0.3.00 62.8% *	Symblepharon 61% * Ankyloblepharon 14% * Persistent epithelial defects 13% * Limbitis 28% *	Mondino and Brown Stage I 3.7% * Stage II 19.6% * Stage III 34% * Stage IV 42.4% * Foster Stage I 2.2% * Stage II 22.7% * Stage III 61% * Stage IV 14% *	Oral 44% Skin 17% Pharynx 33% Anal 5% Genital 5%	-
Demers P et al, 1998 (54)	-	-	-	-	-	Oral 20%	-
Messmer E et al, 2000 (25)	-	-	≥1.00 0% * ≥0.30 <1.00 50% * <0.30 50% *	Trichiasis 44% Symblepharon 83% Ankyloblepharon 17% Persistent epithelial defects 44%	Foster Stage III 83% Stage IV 17%	-	-
Letko E, et al, 2001 (35)	-	-	-	-	-	Oral 33.3% Larynx 16.6% Pharynx 16.6% Genital 16.6%	-
Miserocchi E, et al, 2002 (36)	-	-	≥1.00 7% * ≥0.30 <1.00 36% * <0.3.00 57% *	Punctate keratitis 33% * Persistent epithelial defects 10% * Infectious keratitis 1.6%*	Foster Stage II 34% * Stage III 60% *	Oral 29.5% Skin 16.3% Larynx 18%	-
Letko E, et al, 2002 (55)	-	-	≥1.00 3.5% * ≥0.30 <1.00 28.5% * <0.30 14.2% *	-	-	Oral 57.1% Larynx 14.2% Pharynx 14.2% Genital 28.5%	-

Study	Prevalence	Incidence	Visual acuity BCVA (LogMAR)	Ocular manifestations and complications	Classification	Extraocular involvement	Risk of OMMP
Thorne JE, et al, 2004 (37)	-	-	Me 0.40 (min -0.10 - max ≥3.00)	Trichiasis 42.5%	-	Skin 32.4% Larynx 5.4% Pharynx 82.4%	0.05 per person-year in 5 years
Rauz S, et al, 2005 (26)	-	-	-	Mild conjunctival inflammation 77.70% Moderate/severe conjunctival inflammation 22.20%	-	Oral 55.6% Skin 22.2% Pharynx 27.8% Genital 2.8%	-
Thorne JE, et al, 2006 (49)	-	-	-	Schirmer test 22.7% *	-	-	-
Thorne JE, et al, 2008, (27)	-	-	Me 0.18	Trichiasis 38.5% * Punctate keratitis 21% * Persistent epithelial defects 13.4% * Schirmer test 27.6% *	Foster Stage I 7.6% * Stage II 12% * Stage III 74.5% * Stage IV 2.2% *	Oral 58.3% Skin 12.6%	-
Williams GP, et al, 2011 (38)	-	-	≥1.00 11.1% ≥0.30 <1.00 8.3% <0.30 80.6%	-	Foster Stage IV 3.9%	Oral 40% Skin 18%	-
Mameletzi E, et al, 2012 (39)	-	-	-	Trichiasis 92% Entropion 92% Persistent epithelial defects 61.5% Central opacities/ Neovascularization 15.3%		-	-
Nottage J, et al, 2013 (46)	-	-	Me 0.4 (min 0.13 - max 0-.63)	-	Foster Stage I 0% Stage II 21.7% Stage III 76.1% Stage IV 2.2%	Oral 43.5%	-
Miserocchi E, et al, 2014 (50)	-	-	-	-	Foster Stage III 100%	-	-

Study	Prevalence	Incidence	Visual acuity BCVA (LogMAR)	Ocular manifestations and complications	Classification	Extraocular involvement	Risk of OMMP
Brunner M, et al, 2014 (40)	-	-	-	Symblepharon 58.3%*	Mondino and Brown Stage I 38.8%* Stage II 30.5%* Stage III 19.4%* Stage IV 11.1%* Foster Stage I 27.7%* Stage II 13.8%* Stage III 58.3%* Stage IV 0%*	Oral 11.1% Skin 1% Pharynx 22.2%	-
Goldich Y, et al, 2015 (41)	-	-	≥1.00 6.20%*	Trichiasis 43.9%* Symblepharon 65.6% Ankyloblepharon 4.6%	Foster Stage I 7.8% Stage II 21.8% Stage III 65.6% Stage IV 4.6%	Oral 26.5% Skin 11.7%	-
Williams GP, et al, 2016 (28)	-	-	≥1.00 4% ≥0.30 <1.00 4% <0.30 91%	-	-	Oral 40% Skin 40%	-
Szabó E, et al, 2016 (29)	-	-	-	Trichiasis 27% Entropion 3.9% Symblepharon 15.6%	-	-	-
Long Q, et al, 2016 (56)	-	-	≥1.00 29.10%* ≥0.30 <1.00 33.3%* <0.30 37.5%*	-	Foster Stage I 12.5%* Stage II 4.1%* Stage III 75%* Stage IV 8.3%*	Oral 58.3%	-
Labowsky MT, et al, 2017 (30)	-	-	-	-	Foster Stage I 27% Stage II 13% Stage III 58% Stage IV 2%	Oral 52.7% Skin 27.3%	-

Study	Prevalence	Incidence	Visual acuity BCVA (LogMAR)	Ocular manifestations and complications	Classification	Extraocular involvement	Risk of OMMP
Bobba S et al, 2018 (42)	-	0.7 per million people	<0.30 11%	Moderate/severe Conjunctival inflammation 22%* Trichiasis 39%* Entropion 22%* Symblepharon 44%* Ankyloblepharon 28%* Punctate keratitis 11.1%* Persistent epithelial defects 6%* Limbitis 17%* Infectious keratitis 6%* Central opacities/ Neovascularization 11%*	Mondino and Brown Stage I 33%* Stage II 28%* Stage III 17%* Stage IV 6%*	-	-
Ong HS et al, 2018 (53)	-	-	-	-		Oral 26% Pharynx 13.6%	-
Hong G et al, 2019 (53)	-	-	-	Trichiasis 60.6%*	-	Oral 89.7 Skin 35.8	0.014 per person-year
Fremont F et al, 2019 (43)	-	-	≥1.00 41%* ≥0.30 <1.00 15%* <0.30 44%*	-	Tauber Stage I 9% * Stage IIa 21% * Stage IIb 29% * Stage IIc 0% * Stage IId 0% * Stage IIIa 8% * Stage IIIb 21% * Stage IIIc 18% * Stage IIId 0% * Stage IV 3% *	Oral 41% Skin 12% Pharynx 6%	-
Mendez-Bermudez et al, 2020 (52)	-	-	-	Trichiasis 50%*	Foster Stage III 100% *	Oral 87.5% Skin 50% Larynx 25% Genital 12.5%	-
Coco G et al, 2020 (31)	-	-	-	Trichiasis 28%* Symblepharon 50% Central opacities/ Neovascularization 34%*	-	Oral 28% Skin 6%	-

Study	Prevalence	Incidence	Visual acuity BCVA (LogMAR)	Ocular manifestations and complications	Classification	Extraocular involvement	Risk of OMMP
Alkeraye, et al 2021 (44)	-	-	≥1.00 51.7% * ≥0.30 <1.00 38.4% * <0.30 10% *	-	Foster Stage I 10% * Stage II 15% * Stage III 35% * Stage IV 40% *	-	-
Cifuentes-Gonzalez C et al, 2021 (7)	0.22 per million inhabitants	0.24 per million inhabitants	-	-	-	-	-
Morel M et al, 2022 (32)	1.5 - 2.5%	0.0011 - 0.0007%	-	Trichiasis 38% Entropion 15% Symblepharon 77% Punctate keratitis 46% Persistent epithelial defect 37%	-	-	-
Johnson KB et al, 2023 (33)	-	-	-	-	-	Oral 55% Skin 10%	-
Çiftçi MD et al, 2023 (34)	-	-	>1.00 77.7% * ≥0.30 <1.00 22.7% * <0.30 0% *	Entropion 22.7% Persistent epithelial defect 36.3%	Tauber Stage I 0% * Stage IIa 4.5% * Stage IIb 9% * Stage IIc 0% * Stage IId 18.1% * Stage IIIa 13.6% * Stage IIIb 4.5% * Stage IIIc 0% * Stage IIId 18.1% * Stage IV 31.8% *	Oral 27.2% Skin 18%	-

BCVA: Best Corrected Visual Acuity, logMAR: Logarithm of the Minimum Angle of Resolution, Me: Median, min: Minimum value, max: Maximum value

* Eyes