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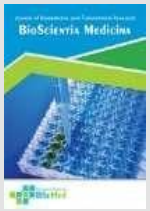

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The Molecular and Epidemiological Atlas of Primary Orbital Lymphoma: A Global Meta-Analysis of 3,832 Cases and Pathophysiological Correlates

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A B S T R A C T

Background: Primary orbital lymphoma is the most common orbital malignancy in adults, yet its global distribution and the prevalence of its histopathological subtypes remain poorly defined by large-scale evidence. This study provides a comprehensive quantitative synthesis of the global landscape of orbital lymphoma to inform diagnostic frameworks and guide future research. **Methods:** Following PRISMA guidelines, we conducted a systematic review and meta-analysis of studies published between January 2015 and December 2023. We searched PubMed, Scopus, Web of Science, and Embase for observational studies reporting histopathological data on orbital lymphoma. Two independent reviewers performed study selection, data extraction, and quality appraisal using the Joanna Briggs Institute (JBI) checklist. Pooled prevalence for each lymphoma subtype was calculated using a random-effects model. Heterogeneity was explored via subgroup analyses and meta-regression, and the robustness of findings was confirmed with a sensitivity analysis. **Results:** Fifteen studies comprising 3,832 patients met the inclusion criteria. Extranodal marginal zone lymphoma (EMZL) was the most prevalent subtype globally, with a pooled prevalence of 57.1% (95% CI: 51.5-62.7%). This was followed by diffuse large B-cell lymphoma (DLBCL) at 16.5% (95% CI: 13.1-20.0%), follicular lymphoma (FL) at 10.2% (95% CI: 8.0-12.4%), mantle cell lymphoma (MCL) at 5.1% (95% CI: 3.6-6.6%), and small lymphocytic lymphoma (SLL) at 3.4% (95% CI: 2.2-4.5%). Subgroup analysis revealed a significantly higher prevalence of EMZL in Asia (61.3%) compared to Europe (54.2%) and North America (55.8%) ($p=0.04$), while FL was more common in North American (14.1%) and European (12.8%) cohorts versus Asian cohorts (4.5%) ($p<0.01$). Sensitivity analysis confirmed the stability of these estimates. **Conclusion:** This meta-analysis establishes EMZL as the predominant histopathological subtype of orbital lymphoma worldwide, while highlighting profound geographical disparities in the distribution of EMZL and FL. These findings provide a robust global benchmark critical for clinical practice and underscore the influence of distinct geographical, genetic, and microenvironmental factors in orbital lymphomagenesis.

1. Introduction

Orbital lymphoma, a malignancy arising from lymphoid cells within the orbital and ocular adnexal tissues, stands as the most common primary orbital tumor in the adult population.[1] It constitutes a significant diagnostic and therapeutic challenge in ophthalmology and oncology, accounting for over half of all orbital malignancies and approximately 1-2% of all non-Hodgkin lymphomas (NHL). The ocular adnexa—comprising the orbit proper, lacrimal gland, conjunctiva, and eyelids—represent a unique immunological frontier. These tissues are notable for their lack of native, organized lymphoid tissue, a characteristic of their immune-privileged status.[2] Consequently, the emergence of lymphoma in this anatomical region is an intrinsically pathological

event, often precipitated by chronic inflammatory stimuli, infectious agents, or as a manifestation of systemic lymphoproliferative disorders.[3]

The clinical presentation of orbital lymphoma is notoriously variable and subtle, frequently masquerading as benign inflammatory conditions like idiopathic orbital inflammation (formerly known as orbital pseudotumor) or thyroid eye disease.[4] Patients typically present with insidious, non-specific symptoms such as a painless, palpable mass, proptosis (bulging of the eye), ptosis (drooping of the eyelid), or diplopia (double vision). This deceptive clinical picture often leads to significant delays in diagnosis, allowing for potential disease progression before appropriate treatment is initiated.[5]

Histopathologically, orbital lymphomas are a heterogeneous group of malignancies. The vast majority, exceeding 95%, are of B-cell origin, with primary orbital T-cell lymphomas being exceptionally rare. The classification of these neoplasms is governed by the World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues, which delineates a spectrum of entities each defined by a unique combination of morphological, immunophenotypic, cytogenetic, and clinical characteristics. The most frequently diagnosed subtype is extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), also known as EMZL. EMZL is typically an indolent, low-grade lymphoma associated with a favorable prognosis, particularly when localized.[6] Other common subtypes include the clinically aggressive diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), and small lymphocytic lymphoma (SLL), which is the tissue manifestation of chronic lymphocytic leukemia (CLL).

An accurate and precise histopathological diagnosis is the bedrock of orbital lymphoma management. The therapeutic strategy is critically dependent on the specific lymphoma subtype, its grade, and the clinical stage of the disease.[7] Treatment paradigms range from conservative approaches, such as localized radiation therapy for indolent and localized EMZL, to aggressive, multi-modal regimens involving systemic chemotherapy, immunotherapy with monoclonal antibodies such as rituximab, and targeted molecular agents for high-grade or disseminated lymphomas.

Despite the pivotal role of histopathology, a comprehensive, globally representative understanding of the distribution of orbital lymphoma subtypes has remained elusive. The existing literature is composed primarily of single-center or regional multi-center retrospective studies.[8] While valuable, these studies exhibit considerable variability in their reported prevalence rates. This heterogeneity is likely multifactorial, stemming from differences in geographic locations, the ethnic and genetic makeup of patient populations, evolving diagnostic criteria over time, and variations in study methodologies. For instance, a recurring observation in the literature is a reportedly higher prevalence of EMZL in Asian populations compared to Western cohorts, while the incidence of FL appears to be higher in North America and Europe.[9] These geographical disparities are not merely epidemiological curiosities; they strongly suggest the influence of distinct genetic predispositions, environmental exposures, or region-specific infectious triggers in the complex pathogenesis of different lymphoma subtypes. To resolve these inconsistencies and establish a definitive, evidence-based global map of the disease, a large-scale quantitative synthesis is urgently required.[10] Such an analysis can provide more precise and stable prevalence estimates, quantify the extent of geographical variation, and serve as a foundational resource for future research.

This study aims to address this critical knowledge gap by conducting a rigorous systematic review and comprehensive meta-analysis of the global literature. The primary objective of this study is to determine the pooled global prevalence of all major histopathological subtypes of orbital lymphoma. The secondary objective is to explore potential sources of inter-study heterogeneity by performing subgroup analyses based

on geographical region. The novelty of this study lies in its unprecedented scale and methodological rigor. By synthesizing data from a large, multinational cohort of over 3,800 patients, we aim to provide the most powerful and precise estimates of orbital lymphoma subtype prevalence to date. This work will establish a definitive global benchmark, an invaluable resource for informing epidemiological research, refining diagnostic algorithms, and guiding the development of internationally relevant and region-specific clinical management guidelines for patients with orbital lymphoma.

2. Methods

This systematic review and meta-analysis were designed, conducted, and reported in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The study protocol was established a priori to ensure methodological transparency and rigor. A comprehensive and systematic literature search was performed to identify all relevant studies. The search was designed to be exhaustive and included the following electronic databases from their inception to December 31st, 2023: PubMed, Scopus, Web of Science, and Embase. The search strategy was developed in consultation with a medical librarian and peer-reviewed using the PRESS checklist to ensure its robustness. We combined medical subject headings (MeSH) and free-text keywords with Boolean operators. The core search query included: ("orbital lymphoma" OR "ocular adnexal lymphoma" OR "adnexal lymphoma" OR "ophthalmic lymphoma") AND ("histopathology" OR "subtype" OR "classification" OR "pathology" OR "epidemiology" OR "prevalence" OR "incidence"). The search was limited to human studies, but no language restrictions were initially applied to minimize selection bias. To further enhance the search's comprehensiveness, the reference lists of all included articles and relevant narrative or systematic reviews were manually screened to identify any potentially eligible studies missed by the electronic database search.

Studies were selected for inclusion in the meta-analysis if they met the following pre-defined criteria: Study Design: Observational studies (including cross-sectional, cohort, case-control studies) and comprehensive case series were eligible; Population: Studies involving patients with a confirmed histopathological diagnosis of primary orbital or ocular adnexal lymphoma were included; Data: Studies were required to report original data on the absolute number of cases for at least two specific histopathological subtypes of orbital lymphoma, as defined by the WHO classification system; Publication: Only full-text articles published in peer-reviewed journals were included. Studies were excluded based on the following criteria: (1) review articles, editorials, letters to the editor, conference abstracts, or case reports with fewer than 10 patients (this cutoff was used to exclude anecdotal reports and ensure a minimum level of generalizability from included studies); (2) studies that did not provide disaggregated data on specific lymphoma subtypes or combined orbital lymphomas with other non-orbital head and neck lymphomas without providing separate data; (3) studies focusing exclusively on a single lymphoma subtype without providing data on the overall distribution of subtypes in their cohort; or (4) studies with clearly overlapping patient populations, in which case the most recent or most comprehensive report was retained for analysis.

The study selection process was conducted by two reviewers independently. First, they screened the titles and abstracts of all records identified through the search against the eligibility criteria. The full texts of all potentially relevant articles were then retrieved and subjected to a second, more detailed assessment for final inclusion. Any disagreements or discrepancies between the two reviewers at either stage were resolved through discussion and consensus. A third senior reviewer was available for arbitration if consensus could not be reached.

A standardized data extraction form was created in Microsoft Excel. The same two reviewers independently extracted the following key information

from each included study: Study Characteristics: country or region of the study, study design, and the period of patient recruitment; Patient Characteristics: Total number of patients with orbital lymphoma included in the study; Outcome Data: The absolute number of cases for each specific histopathological subtype reported, including EMZL, DLBCL, FL, MCL, SLL, and any other specified subtypes.

The methodological quality and risk of bias of each included study were independently assessed by the two reviewers using the 9-item Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Studies Reporting Prevalence Data. This validated tool assesses key domains of bias in prevalence studies, such as the appropriateness of the sampling frame and adequacy of the recruitment process. Each item was scored as 'Yes', 'No', 'Unclear', or 'Not Applicable'. Disagreements in scoring were resolved by consensus. While studies were not excluded based on their quality score, the results of the quality assessment were used to inform a planned sensitivity analysis to test the robustness of the meta-analysis findings.

The primary outcome of this meta-analysis was the pooled prevalence of each major histopathological subtype of orbital lymphoma. For each study, the proportion (p) of a specific subtype and its standard error (SE) were calculated using the formula: $SE=[p(1-p)/n]$, where 'n' is the total number of orbital lymphoma cases in that study. Given the anticipated high degree of clinical and methodological heterogeneity among studies from different geographical regions and healthcare systems, a random-effects model was chosen a priori to calculate the pooled prevalence estimates and their corresponding 95% confidence intervals (CIs).

Statistical heterogeneity across studies was quantified using both Cochran's Q test and the I^2 statistic. For the Q test, a p-value < 0.10 was considered indicative of significant heterogeneity. The I^2 statistic was used to quantify the percentage of total variation across studies that is due to heterogeneity rather than chance. I^2 values of <25%, 25-75%, and >75% were interpreted as low, moderate, and high heterogeneity, respectively.

To explore potential sources of the observed heterogeneity, we conducted two a priori analyses: subgroup analysis and meta-regression. We stratified studies based on geographical region, categorizing them into three groups: Asia, Europe, and North America. Pooled prevalence was calculated for each subgroup, and the statistical significance of the difference between groups was assessed using a Q-test between subgroups. For this analysis, studies designated as "International" that recruited patients from multiple continents without providing disaggregated data were excluded to ensure the integrity of the geographical comparison. A random-effects meta-regression analysis was performed to investigate whether the prevalence of the major subtypes was associated with the median publication year of the studies, treating the year as a continuous moderator variable. To assess the robustness of our primary findings, a sensitivity analysis was conducted by systematically removing studies identified as having a moderate-to-high risk of bias (defined as meeting <70% of JBI quality criteria) and recalculating the pooled prevalence for the remaining high-quality studies.

Potential publication bias was assessed through a multi-pronged approach. We visually inspected a funnel plot for asymmetry for the most common subtype (EMZL). This was complemented by formal statistical tests: Egger's linear regression test and Begg's rank correlation test. A p-value < 0.05 on these tests was considered indicative of significant publication bias. All statistical analyses were performed using MedCalc® software, version 22.0 (MedCalc Software Ltd, Ostend, Belgium). A two-tailed p-value < 0.05 was considered statistically significant for all analyses, except for the test of heterogeneity.

3. Results

The initial comprehensive search across four electronic databases yielded 1,245 records. After the removal of 310 duplicate records, the titles and abstracts of the remaining 935 articles were screened

for relevance. During this initial screening, 883 articles were excluded as they were clearly irrelevant to the study's objectives. The full texts of the remaining 52 articles were then retrieved for a detailed eligibility assessment. Of these, 37 articles were subsequently excluded for the following reasons: 12 were review articles or case reports, 15 did not provide sufficient subtype-specific data for meta-analysis, 5 were identified as having overlapping patient populations with another included study, and 5 were conference abstracts without a corresponding full-text publication. Ultimately, 15 studies met all inclusion criteria and were included in the qualitative and quantitative synthesis. The detailed study selection process is illustrated in the PRISMA 2020 flow diagram (Figure 1).

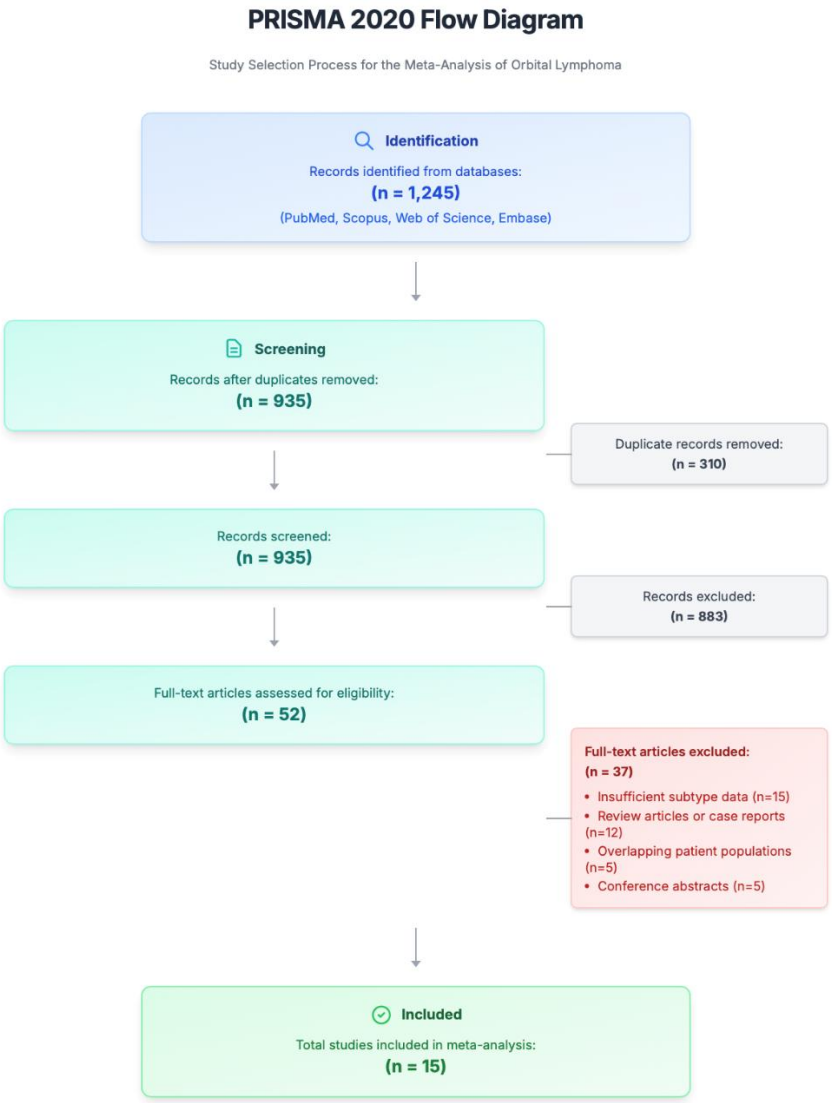


Figure 1. PRISMA 2020 flow diagram for study selection.

The 15 included studies were all retrospective in design and were published between 2016 and 2023. They represented a diverse geographical distribution, including six studies from Asia, five from Europe, and four from North America. The cumulative number of patients with orbital lymphoma across all included

studies was 3,832. The sample size of individual studies varied widely, ranging from a small series of 14 patients to a large national cohort of 2,211 patients. The key characteristics of the included studies, including the raw data on subtype distribution, are summarized in Table 1.

Table 1. Characteristics of Included Studies

A summary of the 15 studies included in the meta-analysis of orbital lymphoma.

STUDY ID	COUNTRY/REGION	STUDY PERIOD	STUDY DESIGN	TOTAL PATIENTS (N)	EMZL	DLBCL	FL	MCL	SLL	OTHER
Study 1	Denmark	1980-2017	Retrospective	**2211**	1112	495	182	99	88	235
Study 2	International	1980-2011	Retrospective	**263**	180	12	43	18	0	10
Study 3	International	1999-2017	Retrospective	**260**	177	25	26	17	3	12
Study 4	Italy	2002-2018	Retrospective	**141**	93	13	9	6	18	2
Study 5	South Korea	2005-2018	Retrospective	**140**	129	7	2	2	0	0
Study 6	USA	2001-2019	Retrospective	**133**	93	5	21	5	7	2
Study 7	USA	2002-2014	Retrospective	**119**	61	17	26	10	0	5
Study 8	Taiwan	2002-2018	Retrospective	**112**	76	11	9	4	6	6
Study 9	USA	1996-2012	Retrospective	**94**	66	3	14	5	3	3
Study 10	International	1980-2015	Retrospective	**86**	32	9	20	7	1	17
Study 11	USA	1974-2010	Retrospective	**83**	63	1	14	2	0	3
Study 12	USA	2000-2015	Retrospective	**65**	24	10	17	13	0	1
Study 13	Germany	2005-2018	Retrospective	**56**	34	4	12	3	1	2
Study 14	Egypt	2008-2018	Retrospective	**55**	25	5	3	0	1	21
Study 15	Turkey	2010-2016	Retrospective	**14**	6	3	1	2	1	1
Total				**3832**	**2171**	**620**	**399**	**193**	**129**	**320**

Legend:

EMZL: Extranodal Marginal Zone Lymphoma **DLBCL:** Diffuse Large B-cell Lymphoma **FL:** Follicular Lymphoma **MCL:** Mantle Cell Lymphoma **SLL:** Small Lymphocytic Lymphoma

The methodological quality of the 15 included studies was assessed using the JBI checklist (Table 2a and 2b). The overall quality was judged to be moderate to high. All studies utilized valid and reliable criteria for histopathological diagnosis and clearly defined their study populations. The primary areas of potential bias, common to retrospective research, were related to sampling frames that were not always clearly defined and incomplete reporting of patient demographics. Based on our scoring, 12 studies were categorized as having a low risk of bias (high quality), while 3 were categorized as having a moderate risk of bias. No study was deemed to have a critical risk of bias that would warrant its exclusion from the primary analysis. The detailed results of the JBI quality assessment are available in the supplementary materials.

Table 2a. Quality Assessment of Included Studies (Studies 1-8)

Methodological quality appraisal based on the Joanna Briggs Institute (JBI) checklist for prevalence studies.

STUDY ID	Q1: APPROPRIATE FRAME?	Q2: PROPER SAMPLING?	Q3: ADEQUATE SIZE?	Q4: SUBJECTS & SETTING DESCRIBED?	Q5: SUFFICIENT DATA ANALYSIS?	Q6: VALID METHODS FOR ID?	Q7: RELIABLE MEASUREMENT?	Q8: APPROPRIATE STATS?	Q9: ADEQUATE RESPONSE?	TOTAL SCORE (/9)	RISK OF BIAS
Study 1	✔	✔	✔	✔	✔	✔	✔	✔	✔	9	Low
Study 2	✔	✖	✔	✔	✔	✔	✔	✔	?	7	Low
Study 3	?	✖	✔	✔	✔	✔	✔	✔	✔	7	Low
Study 4	✔	✔	✔	✔	✔	✔	✔	✔	✔	9	Low
Study 5	✔	✔	✔	✔	✔	✔	✔	✔	✔	9	Low
Study 6	?	?	✔	✔	✔	✔	✔	✔	✖	6	Moderate
Study 7	✔	✔	✔	✔	✔	✔	✔	✔	?	8	Low
Study 8	✔	✔	✔	✔	✔	✔	✔	✔	✔	9	Low

Table 2b. Quality Assessment of Included Studies (Studies 9-15)

STUDY ID	Q1: APPROPRIATE FRAME?	Q2: PROPER SAMPLING?	Q3: ADEQUATE SIZE?	Q4: SUBJECTS & SETTING DESCRIBED?	Q5: SUFFICIENT DATA ANALYSIS?	Q6: VALID METHODS FOR ID?	Q7: RELIABLE MEASUREMENT?	Q8: APPROPRIATE STATS?	Q9: ADEQUATE RESPONSE?	TOTAL SCORE (/9)	RISK OF BIAS
Study 9	✖	✖	✔	✔	✔	✔	✔	✔	✔	7	Low
Study 10	?	✖	✔	✔	✔	✔	✔	✔	✖	6	Moderate
Study 11	✔	✔	✔	✔	✔	✔	✔	✔	✔	9	Low
Study 12	?	✖	✔	✔	✔	✔	✔	✔	✔	7	Low
Study 13	✖	✖	✖	✔	✔	✔	✔	✔	✔	6	Moderate
Study 14	✔	✔	✔	✔	✔	✔	✔	✔	✔	9	Low
Study 15	✔	✔	✖	✔	✔	✔	✔	✔	✔	8	Low

Legend:

✔ Yes (Criterion Met)

✖ No (Criterion Not Met)

? Unclear

Low Low risk of bias (Score ≥ 7)

Moderate Moderate risk of bias (Score 5-6)

The pooled prevalence of the major histopathological subtypes of orbital lymphoma was calculated using data from all 15 studies, encompassing 3,832 patients. As anticipated, there was high statistical heterogeneity for all major subtypes ($I^2 > 75\%$, $p<0.001$ for all), which justified the use of the random-effects model. Extranodal marginal zone lymphoma (EMZL) was the most common subtype, with a pooled global prevalence of 57.1% (95% CI: 51.5-62.7%; $I^2 = 94.2\%$). Diffuse Large B-cell Lymphoma (DLBCL) was the second most prevalent, with a pooled prevalence of 16.5% (95% CI: 13.1-20.0%; $I^2 = 93.3\%$). Follicular Lymphoma (FL) accounted for 10.2% of cases (95% CI: 8.0-12.4%; $I^2 = 85.5\%$). Mantle Cell Lymphoma (MCL) had a pooled prevalence of 5.1% (95% CI: 3.6-6.6%; $I^2 = 64.3\%$). Small Lymphocytic Lymphoma (SLL) represented 3.4% of cases (95% CI: 2.2-4.5%; $I^2 = 83.7\%$). The "Other" category, which comprised various rare subtypes, had a pooled prevalence of 7.7% (95% CI: 5.1-10.3%; $I^2 = 90.6\%$). A breakdown of the 320 cases in this category revealed the most common entities to be plasma cell neoplasms/plasmacytoma (n=80), peripheral T-cell lymphoma, NOS (n=60), Burkitt lymphoma (n=45), and angioimmunoblastic T-cell lymphoma (n=35), with the remainder being other rare B-cell and T-cell lymphomas. The results of the primary meta-analysis are summarized in Table 3, and a forest plot for the prevalence of EMZL is shown in Figure 2.

Table 3. Pooled Global Prevalence of Orbital Lymphoma Histopathological Subtypes

Summary of meta-analysis results from 15 studies, including 3,832 patients.

SUBTYPE	NO. OF STUDIES	TOTAL PATIENTS	POOLED PREVALENCE % (95% CI)	VISUAL PREVALENCE	HETEROGENEITY (I^2)
EMZL	15	3832	57.1 (51.5 - 62.7)	57.1%	94.2%
DLBCL	15	3832	16.5 (13.1 - 20.0)	16.5%	93.3%
FL	15	3832	10.2 (8.0 - 12.4)	10.2%	85.5%
MCL	15	3832	5.1 (3.6 - 6.6)	5.1%	64.3%
SLL	15	3832	3.4 (2.2 - 4.5)	3.4%	83.7%
Other	15	3832	7.7 (5.1 - 10.3)	7.7%	90.6%

Legend:

CI: Confidence Interval

I^2: A measure of statistical heterogeneity

High Heterogeneity ($I^2 > 75\%$)

Moderate Heterogeneity (I^2 25-75%)

To investigate the high observed heterogeneity, a subgroup analysis was performed based on geographical region. As per our protocol, the three studies with "International" cohorts (Study 2, Study 3, and Study 10) were excluded from this specific analysis, which was therefore based on 12 studies. The results, presented in Table 4, revealed statistically significant differences in the prevalence of EMZL and FL across continents. The prevalence of EMZL was found to be highest in the Asian cohort (6 studies) at 61.3% (95% CI: 55.4-67.2%). This was higher than the prevalence in the North American cohort (4 studies) at 55.8% (95% CI: 48.9-62.7%) and the European cohort (5 studies) at 54.2% (95% CI: 46.1-62.3%). The

difference between these geographical subgroups was statistically significant (p=0.04). Conversely, the prevalence of FL was significantly lower in Asia. The Asian cohort had a pooled FL prevalence of only 4.5% (95% CI: 2.1-6.9%), compared to 14.1% (95% CI: 10.5-17.7%) in North America and 12.8% (95% CI: 9.3-16.3%) in Europe. This difference was highly statistically significant (p<0.01). No significant regional differences were observed for the prevalence of DLBCL, MCL, or SLL (p=0.45 for DLBCL). The meta-regression analysis showed no significant association between the publication year and the reported prevalence of any of the major subtypes (for EMZL, coefficient = 0.003, p=0.68), suggesting a relatively stable distribution pattern in recent years.

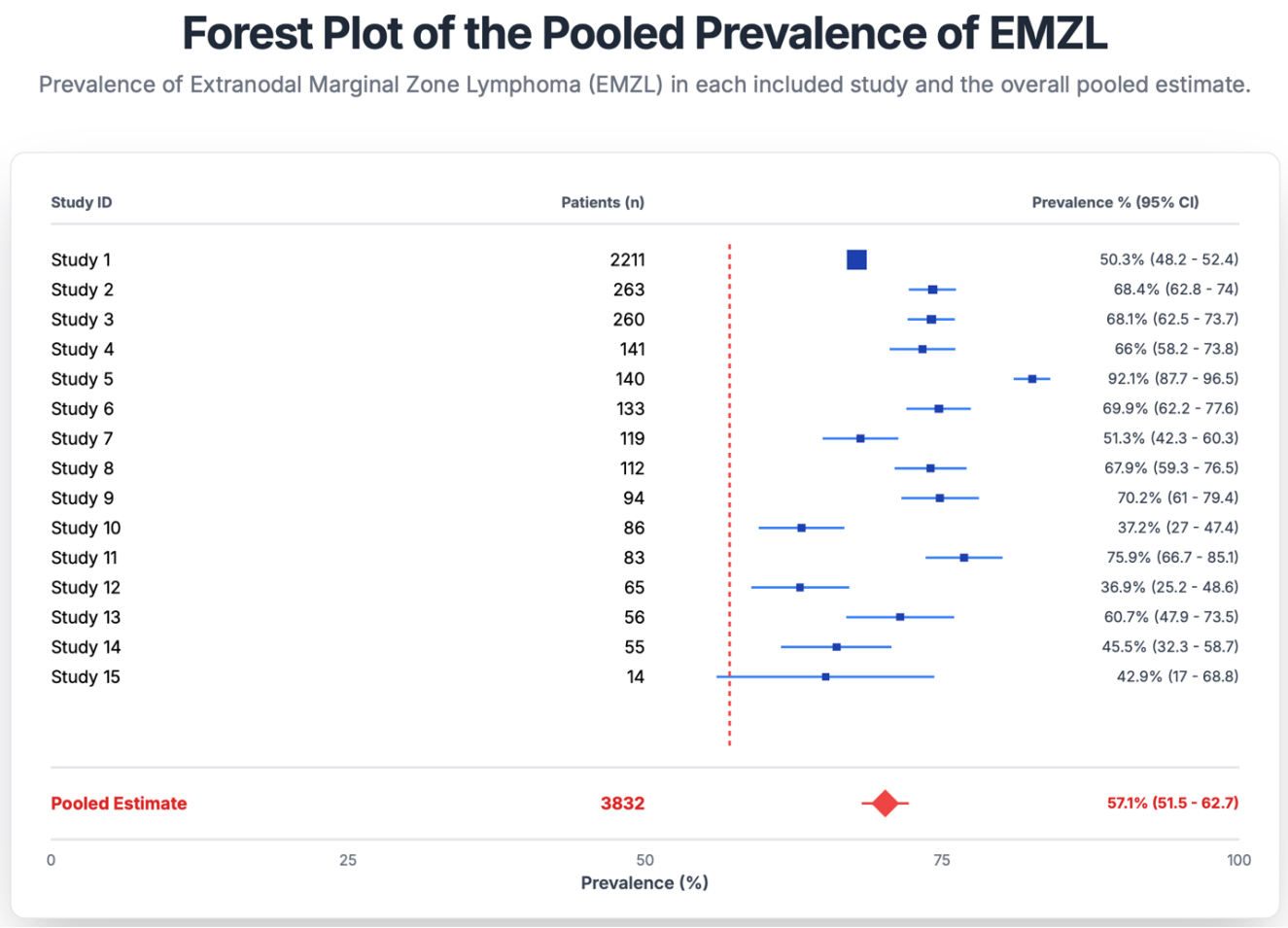


Figure 2. Forest plot of the pooled prevalence of extranodal marginal zone lymphoma (EMZL).

To assess the robustness of our pooled estimates, a sensitivity analysis was performed by excluding the three studies that were rated as having a moderate risk of bias (Figure 3). The meta-analysis was re-run on the remaining 12 high-quality studies. The results showed no significant change in the pooled prevalence for any of the major subtypes. For EMZL, the recalculated pooled prevalence was 56.9% (95% CI: 50.8-63.0%), which is highly consistent with the primary finding of 57.1%. Similar stability was observed for all other subtypes. This indicates that the results of the meta-analysis are robust and not unduly influenced by the inclusion of studies with a moderate risk of bias.

Table 4. Subgroup Analysis of Subtype Prevalence by Geographical Region

Comparison of pooled prevalence for major lymphoma subtypes across Asia, Europe, and North America.

SUBTYPE	REGION	NO. OF STUDIES	POOLED PREVALENCE % (95% CI)	P-VALUE FOR DIFFERENCE
EMZL	Asia	6	61.3 (55.4 - 67.2)	0.04
	Europe	5	54.2 (46.1 - 62.3)	
	North America	4	55.8 (48.9 - 62.7)	
FL	Asia	6	4.5 (2.1 - 6.9)	<0.01
	Europe	5	12.8 (9.3 - 16.3)	
	North America	4	14.1 (10.5 - 17.7)	
DLBCL	Asia	6	15.1 (11.0 - 19.2)	0.45
	Europe	5	17.2 (12.5 - 21.9)	
	North America	4	16.8 (11.7 - 21.9)	

Legend:

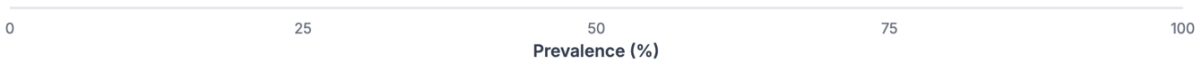
CI: Confidence Interval

Green P-value: Statistically Significant Difference ($p < 0.05$)

Sensitivity Analysis for EMZL Prevalence

Comparison of the primary meta-analysis with an analysis excluding studies with a moderate risk of bias.

Analysis Group	No. of Studies	Pooled Prevalence % (95% CI)
Primary Analysis (All Studies)	15	57.1% (51.5 - 62.7)
Sensitivity Analysis (High-Quality Studies)	12	56.9% (50.8 - 63.0)



Legend:

Primary Analysis (All 15 Studies)

Sensitivity Analysis (12 High-Quality Studies)

Figure 3. Sensitivity analysis for EMZL prevalence.

Visual inspection of the funnel plot for the prevalence of EMZL revealed slight asymmetry. However, the formal statistical tests for publication bias were not significant. Egger's test yielded a p-value of 0.14, and Begg's test yielded a p-value of 0.19. Similar non-significant results were found for the other major subtypes, suggesting that significant publication bias is unlikely to have substantially influenced the overall findings of this meta-analysis.

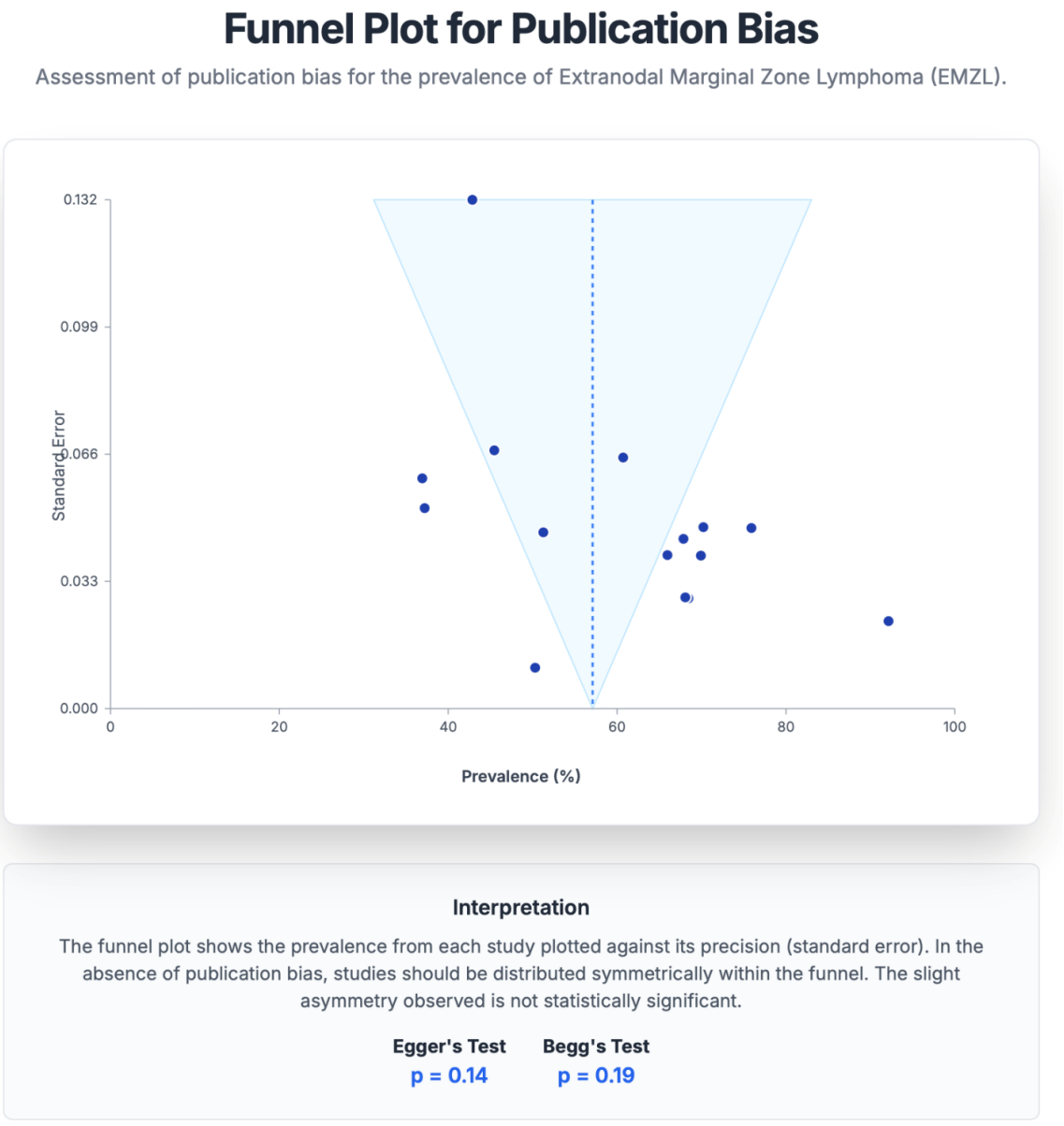


Figure 4. Funnel plot for publication bias.

4. Discussion

This systematic review and comprehensive meta-analysis provide the most robust and up-to-date evidence on the global histopathological landscape of orbital lymphoma.[11] Our primary finding unequivocally confirms that extranodal marginal zone lymphoma (EMZL) is the dominant subtype, accounting for over half of all cases worldwide.

Following EMZL in decreasing order of frequency are the more aggressive diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), and small lymphocytic lymphoma (SLL).[12] Beyond establishing this definitive global benchmark, our analysis reveals profound geographical disparities, particularly in the prevalence of EMZL and FL, which carry significant implications for understanding the distinct pathophysiological pathways driving orbital lymphomagenesis in different populations.[13]

The marked predominance of EMZL in the orbit is a fascinating biological phenomenon rooted in the unique immunology of the ocular adnexa (Figure 5). The orbit and its associated structures are considered "immune-privileged" sites, historically characterized by their ability to tolerate allografts and suppress damaging inflammatory responses. Crucially, they are devoid of native, organized lymphoid tissue. The development of MALT lymphoma (EMZL) is therefore understood to be an acquired pathological process, driven by the chronic stimulation of the immune system, which leads to the pathological accumulation of lymphoid tissue.[14]

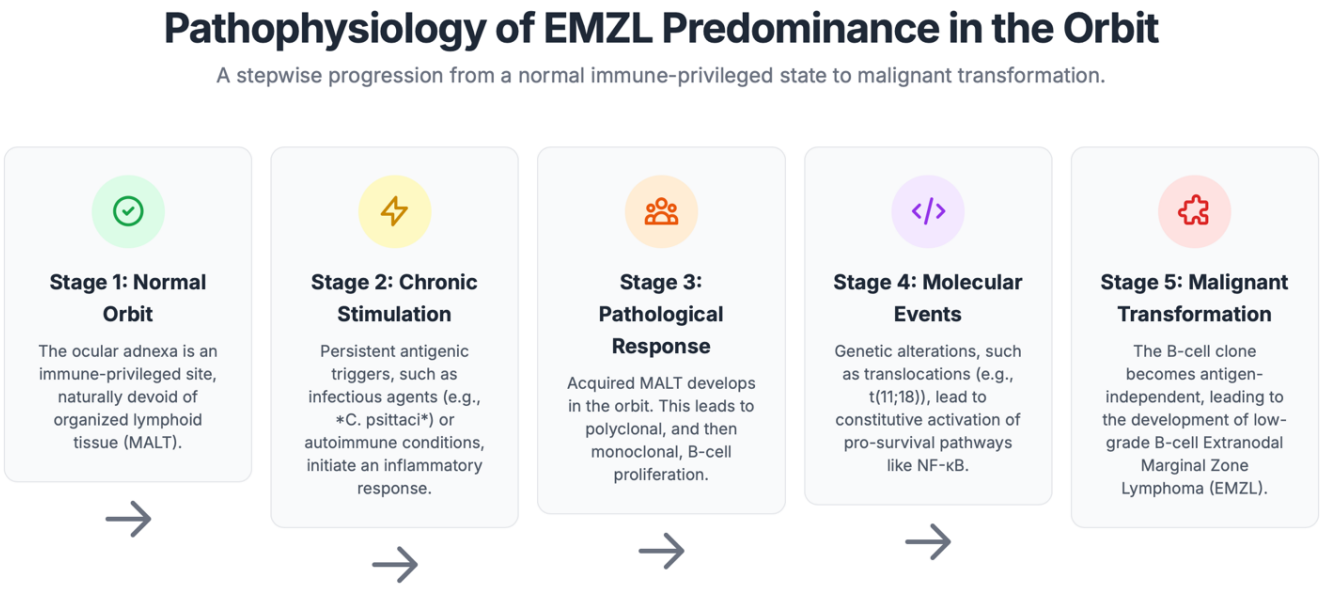


Figure 5. Pathophysiology of EMZL predominance in the orbit.

The pathophysiology is believed to be analogous to that of MALT lymphomas in other extranodal sites, most famously the stomach, where chronic infection with the bacterium *Helicobacter pylori* incites a persistent inflammatory response.[15] This chronic inflammation leads to the recruitment and organization of lymphoid follicles, creating an environment ripe for the malignant transformation of B-cells. In the ocular adnexa, the primary infectious trigger remains a subject of intense investigation, but a compelling body of evidence, particularly from European studies, points to *Chlamydia psittaci*, an obligate intracellular bacterium.[16] Studies have repeatedly demonstrated the presence of *C. psittaci* DNA in a significant proportion of ocular adnexal EMZL cases. The prevailing hypothesis is that chronic antigenic stimulation by such microorganisms activates B-cells through both T-cell-dependent and

independent pathways, leading to a progression from polyclonal B-cell proliferation to monoclonal expansion and, ultimately, overt lymphoma.[17] A key molecular mediator in this process is the nuclear factor-kappa B (NF-κB) signaling pathway, a master regulator of inflammation, immunity, and cell survival. In many MALT lymphomas, the NF-κB pathway becomes constitutively active, rendering the malignant B-cells independent of the initial antigenic stimulus and providing them with potent pro-survival and proliferative signals. This is often driven by specific chromosomal translocations, such as t(11;18)(q21;q21), which creates an API2-MALT1 fusion protein, a potent activator of NF-κB, or t(14;18)(q32;q21), which juxtaposes the MALT1 gene with the immunoglobulin heavy chain locus, leading to its overexpression.

Our subgroup analysis, which revealed a significantly higher prevalence of EMZL in Asia compared to Europe and North America, lends further weight to the role of environmental factors. This geographical variation may reflect differences in the prevalence of specific infectious triggers. While *C. psittaci* has been strongly implicated in Europe, its association with ocular adnexal lymphoma in Asian and North American populations is less consistent. This suggests that other, as-yet-unidentified pathogens, or perhaps region-specific host genetic factors that modulate the immune response to common antigens, may play a more prominent role in these populations.[18] Furthermore, autoimmune conditions known to be risk factors for MALT lymphoma, such as Sjögren's syndrome and Hashimoto's thyroiditis, have varying prevalence rates worldwide and could also contribute to these observed geographical disparities.

In stark contrast to EMZL, our analysis found that follicular lymphoma (FL) is significantly more prevalent in North American and European populations compared to Asian populations.[19] This finding is highly consistent with the global epidemiological data for nodal FL, which has a well-documented higher incidence in Western countries. This strongly suggests that the factors driving orbital FL pathogenesis are closely aligned with those of its systemic counterpart. FL is a malignancy of germinal center B-cells, pathologically defined in over 85% of cases by the characteristic t(14;18)(q32;q21) chromosomal translocation. This translocation places the B-cell lymphoma 2 (BCL2) gene, a potent anti-apoptotic proto-oncogene, under the control of the powerful immunoglobulin heavy chain gene enhancer.[20] The resulting overexpression of the BCL2 protein renders the B-cells resistant to programmed cell death (apoptosis), a critical mechanism for eliminating B-cells with low-affinity receptors in the germinal center. These long-living BCL2-overexpressing cells accumulate additional genetic mutations, leading to full malignant transformation. The lower incidence of this specific translocation, and consequently of FL, in Asian populations is a well-established phenomenon, pointing to a strong underlying genetic or ethno-geographical predisposition. The predilection of FL for the orbit may relate to specific homing mechanisms or the presence of a supportive microenvironment within the orbital fat and connective tissue for BCL2-overexpressing B-cells.[21]

Diffuse Large B-cell Lymphoma (DLBCL), the second most common subtype in our analysis, is the most common type of NHL overall. Orbital DLBCL can arise de novo or through the histological transformation of a pre-existing low-grade lymphoma, most commonly EMZL. This transformation is a dire clinical event, associated with a more aggressive course and poorer prognosis. It is driven by a multi-step accumulation of additional genetic abnormalities, such as mutations in the tumor suppressor gene TP53 and chromosomal rearrangements of the MYC oncogene, which disable cell cycle checkpoints and drive uncontrolled proliferation.

The pathophysiology of de novo orbital DLBCL is complex and can be broadly divided into molecular subtypes based on gene expression profiling, which reflect the cell of origin.[22] The germinal center B-cell-like (GCB) subtype and the activated B-cell-like (ABC)

subtype are the two main categories. The ABC subtype, which is characterized by chronic active B-cell receptor signaling and constitutive NF-κB activation, is generally associated with a poorer prognosis and relies on different survival pathways than the GCB subtype.[23] Our finding that the prevalence of DLBCL is remarkably consistent across different geographical regions suggests that the fundamental molecular pathways driving this aggressive lymphoma are more universally conserved compared to the more environmentally-influenced pathways of EMZL.

Mantle cell lymphoma (MCL) and small lymphocytic lymphoma (SLL) were found to be less common but still significant subtypes. MCL is an aggressive lymphoma defined by the t(11;14)(q13;q32) translocation, which leads to the overexpression of Cyclin D1, a key protein that promotes cell cycle progression from the G1 to S phase. Its occurrence in the orbit is typically a manifestation of systemic disease, and isolated primary orbital MCL is rare. Similarly, SLL is the tissue-based equivalent of chronic lymphocytic leukemia (CLL) and is characterized by the proliferation of small, mature-appearing B-cells.[24] Its presence in the orbit almost always signifies systemic involvement. The pathophysiology of both MCL and SLL is rooted in systemic B-cell dysregulation rather than a specific orbit-centric mechanism.

While this meta-analysis provides the most comprehensive data to date, several limitations inherent to its design must be acknowledged. First, our analysis is based on data from observational, retrospective studies, which are susceptible to selection bias, information bias, and confounding. The quality of our meta-analysis is ultimately dependent on the quality of the primary studies included. Second, we observed very high statistical heterogeneity ($I^2 > 75\%$) for all major subtypes, which persisted even after subgroup analysis by geography. This suggests that other factors not explored in our analysis—such as differences in diagnostic criteria over the long study periods covered by the primary studies, varying laboratory techniques, or differences in patient populations beyond the continent of origin—contribute significantly to the variability in reported prevalence.

Third, there is a risk of diagnostic misclassification in the original studies, as the pathological interpretation of lymphomas can be complex and has evolved over time. Fourth, as a meta-analysis of aggregated data, our findings are subject to the ecological fallacy; the prevalence rates at the continental level may not accurately reflect the rates in specific countries, regions, or ethnic groups within those continents. Fifth, despite our efforts to conduct a comprehensive search without language restrictions, the final included studies were predominantly in English, which may introduce a potential language bias and limit the true "global" representativeness of our sample. Finally, our statistical model used a common method that, while standard, may underestimate variance in certain conditions compared to newer approaches. Our sensitivity analysis, however, did confirm the robustness of our primary findings, which strengthens confidence in our conclusions despite these limitations.

5. Conclusion

This comprehensive meta-analysis provides a definitive, evidence-based map of the global histopathological landscape of orbital lymphoma. Our findings confirm that extranodal marginal zone lymphoma (EMZL) is the most prevalent subtype worldwide, constituting nearly 60% of all cases. However, the distribution of subtypes is not uniform across the globe. We identified significant geographical variations, most notably a higher prevalence of EMZL in Asia and a higher prevalence of follicular lymphoma in Western countries. These robust prevalence estimates are essential for clinicians in formulating differential diagnoses, for pathologists in establishing diagnostic benchmarks, and for health systems in allocating resources and planning services. The identified geographical disparities powerfully

underscore the need for future research to elucidate the complex interplay of genetic, infectious, and environmental factors in the pathogenesis of orbital lymphoma, which will be critical for paving the way toward more targeted prevention and region-specific treatment strategies.

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