• Clinical Research •

Visual prognosis and survival outcomes in patients with ocular adnexal diffuse large B-cell lymphoma

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Abstract

● **AIM:** To investigate the clinical characteristics and treatment outcomes, including visual function and overall survival (OS) of patients with ocular adnexal diffuse large B-cell lymphoma (OA-DLBCL).

● **METHODS:** This retrospective cohort study enrolled 29 patients diagnosed with OA-DLBCL based on histopathological biopsy between 2006 and 2023. Patients were stratified into two subgroups: primary OA-DLBCL (no prior history of lymphoma) and secondary OA-DLBCL (history of DLBCL at non-ocular adnexal sites). OS was defined as the time interval from OA-DLBCL diagnosis to death from any cause. Survival analysis was performed using the Kaplan–Meier method, and prognostic factors affecting OS were identified using multivariate Cox proportional hazards regression with a stepwise selection approach.

● **RESULTS:** The cohort included 24 patients with primary OA-DLBCL (13 males, 11 females; mean age: 61.36±18.29y) and 5 patients with secondary OA-DLBCL (2 males, 3 females; mean age: 50.94±18.17y). Among the primary OA-DLBCL subgroup, 12 patients (50%) presented with advanced disease (Ann Arbor stage IIIE–IV), and 16 patients (66%) were classified as T4 disease according to the tumor-node-metastasis (TNM) staging system. The mean final visual acuity was 1.72±1.10 in the primary group and 0.90±1.18 in the secondary group. The 5-year OS rate for the entire cohort was 27.7%. Multivariate analysis identified five factors significantly associated with poor survival outcomes: epiphora [adjusted hazard ratio (aHR), 36.95], atherosclerotic cardiovascular disease (aHR, 10.08), human immunodeficiency virus (HIV) infection (aHR, 12.47), M1 stage (aHR, 6.99), and secondary OA-DLBCL (aHR, 6.03; all $P<0.05$). The median OS was 1.68y for primary OA-DLBCL and 1.12y for secondary OA-DLBCL.

● **CONCLUSION:** A substantial proportion of patients with primary OA-DLBCL present with advanced-stage disease at diagnosis. Epiphora, atherosclerotic cardiovascular disease, HIV infection, M1 stage, and secondary OA-DLBCL are independent prognostic factors for poor survival outcomes. These findings emphasize the urgent need for optimized therapeutic strategies and early screening protocols to improve the management of OA-DLBCL, particularly in developing countries.

● **KEYWORDS:** ocular adnexal diffuse large B-cell lymphoma; visual prognosis; overall survival; prognostic factors; Ann Arbor staging; tumor-node-metastasis staging

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INTRODUCTION

Ocular adnexal lymphoma (OAL) is a lymphoproliferative disease that affects the orbit, conjunctiva, eyelids, and lacrimal glands, making it the most common orbital malignancy. Non-Hodgkin's lymphoma (NHL) is the predominant type of OAL. Extranodal marginal zone lymphoma of the mucosa-associated lymphoid tissue type is the most common, followed by diffuse large B-cell lymphoma (DLBCL), which constitutes approximately 9% to 19% of orbital lymphomas[1-3]. The primary sites of DLBCL in OAL are the orbit, lacrimal system, and eyelids[3]. DLBCL is the most common form of NHL and accounts for 30% of all NHL cases[4].

The first-line treatment for DLBCL typically involves rituximab combined with an anthracycline-containing regimen of cyclophosphamide, hydroxydaunorubicin, vincristine sulfate, and prednisone (R-CHOP)[5]. This treatment can be

supplemented by radiotherapy and other immunosuppressive drugs. However, in Thailand, the treatment of OA-DLBCL varies, owing to differences in healthcare accessibility and medical schemes.

Despite extensive research on the survival outcomes of DLBCL, there is a paucity of studies focusing on the visual prognosis and survival outcomes of patients with OA-DLBCL in developing countries. This gap in the literature underscores the need for further investigation. Therefore, in this study, we aimed to determine the clinical presentation, visual prognosis, stage, and survival rate of patients with OA-DLBCL in southern Thailand, providing valuable insights into the management and outcomes of this malignancy in a developing country.

PARTICIPANTS AND METHODS

Ethical Approval This retrospective cohort study was conducted at Songklanagarind Hospital, a tertiary university hospital. The study was approved by the Human Research Ethics Committee of the Faculty of Medicine at the Prince of Songkla University (REC 66-029-2-4), in compliance with the Declaration of Helsinki and relevant reporting guidelines. Written informed consent was obtained from the patients.

Participants Patients with biopsy-proven OA-DLBCL diagnosed between January 1, 2006, and June 30, 2023, were included in the study. Patients were classified as having primary OA-DLBCL if they had no history of lymphoma. Those with a history of DLBCL at sites other than the ocular adnexa were classified as secondary OA-DLBCL. The inclusion criterion was a diagnosis of OA-DLBCL based on biopsy results. The exclusion criteria were no definitive biopsy confirmation and incomplete medical records. All the patients were informed of the available treatment options and their potential side effects. Treatment protocols were implemented in accordance with the National Comprehensive Cancer Network (NCCN) guidelines. However, some patients received alternative treatments based on individual fitness status and access to medications.

Data Collection Data were collected retrospectively from medical records and included age, sex, presenting signs and symptoms, disease location, stage according to the American Joint Committee on Cancer (AJCC) eighth edition and Ann Arbor staging system, treatment modality, and overall survival (OS). Information on the date and cause of death was obtained from the Songkhla Cancer Registry and the Bureau of Registration Administration. OS was defined as the date of OAL diagnosis to the date of death from any cause. Patients who survived were censored at the last known follow-up or on October 31, 2023.

Statistical Analysis Statistical analyses were performed using STATA version 14 (StataCorp LP., College Station, TX, USA). The Fisher exact test was used to analyze nominal data, and the Mann-Whitney *U* test was applied to continuous data. OS was defined as the time from OA-DLBCL diagnosis to death from any cause and was analyzed using the Kaplan-Meier method. Factors affecting OS were identified using a multivariate Cox proportional hazards model with a stepwise regression. Statistical significance was set at $P<0.05$.

RESULTS

Patient Demographics and Clinical Characteristics In total, 35 patients were diagnosed with OA-DLBCL at the eye clinic, and 6 were excluded owing to incomplete data, resulting in 29 patients included in the study. Among them, 24 had primary OA-DLBCL, and 5 had secondary OA-DLBCL. The mean patient age was 59y. Initial visual acuity was 1.22±1.06 in primary OA-DLBCL and 0.27±0.17 in secondary OA-DLBCL ($P=0.059$). The primary cause of decreased vision was compressive optic neuropathy (61%). Seventeen patients (58.6%) had Ann Arbor stages III–IV disease. The laterality was predominantly unilateral, affecting 27 patients (93.1%).

Treatment Modalities The patients received various treatments: rituximab with chemotherapy (34.5%), chemotherapy without rituximab (27.5%), and combined chemotherapy with radiotherapy (13.8%; Table 1). Among the five patients who were diagnosed with secondary lymphoma, two underwent orbital radiation for OAL treatment (Table 2).

Visual Acuity and Survival Outcomes After treatment, the final visual acuity for primary OA-DLBCL was 1.72±1.10, and that for secondary OA-DLBCL was 0.90±1.18. The mean follow-up time was 20.4mo (range, 1.7-85.1mo). Nineteen patients died during the follow-up period, and only two patients without human immunodeficiency virus (HIV) infection died from other causes (1 endocarditis and 1 septicemia). The median OS for primary OA-DLBCL was 1.68y, compared to 1.12y for secondary OA-DLBCL. OS and visual acuity outcomes between the observation and treatment groups revealed no significant differences ($P=0.633$ and 0.651, respectively). Treatment with rituximab resulted in slightly better OS than treatment without rituximab or observation, although the difference was not statistically significant (Table 2).

Factors Affecting Survival The log-rank test was used to identify several variables that were significantly associated with OS (Figure 1). No significant difference in tumor size was observed between patients with and without epiphora ($P=0.640$). Multivariate analysis revealed that epiphora, atherosclerotic cardiovascular disease (ASCVD), HIV infection, M1 stage, and secondary OA-DLBCL were independently associated with survival outcomes (Table 3).

DISCUSSION

This study is the largest investigation of OA-DLBCL in Thailand, and it includes 29 patients. Among these, primary

Table 1 Baseline clinical characteristics and treatment modalities of patients with ocular adnexal diffuse large B-cell lymphoma

Clinical characteristics	Total (*n*=29)	Primary (*n*=24)	Secondary (*n*=5)	*P*
Age at diagnosis (y)				
Mean±SD	59.56±18.39	61.36±18.29	50.94±18.17	0.256
Median (min, max)	65.19 (3.58, 84.87)	66.29 (3.58, 84.87)	38.98 (36.98, 74.13)	0.166
Age at diagnosis (y)				
≤60	12 (41.4)	9 (37.5)	3 (60.0)	0.622
>60	17 (58.6)	15 (62.5)	2 (40.0)	
Sex				
Male	15 (51.7)	13 (54.2)	2 (40.0)	0.651
Female	14 (48.3)	11 (45.8)	3 (60.0)	
Duration of symptom (d)				
Median (min, max)	30 (7, 365)	30 (7, 365)	30 (14, 60)	0.636
Laterality				
Unilateral	27 (93.1)	22 (91.7)	5 (100.0)	1.000
Bilateral	2 (6.9)	2 (8.3)	0	
Symptoms and signs				
Periocular swelling	15 (51.7)	13 (54.2)	2 (40.0)	0.651
Proptosis	13 (44.8)	12 (50.0)	1 (20.0)	0.343
Ocular pain	10 (34.5)	10 (41.7)	0	0.134
Decreased vision	14 (48.3)	12 (50.0)	2 (40.0)	1.000
Diplopia	6 (20.7)	5 (20.8)	1 (20.0)	1.000
Conjunctival salmon patch	1 (3.5)	1 (4.2)	0	1.000
Ptosis	5 (17.2)	4 (16.7)	1 (20.0)	1.000
Epiphora	4 (13.8)	4 (16.7)	0	1.000
B symptoms	0	0	0	-
High intraocular pressure	3 (10.3)	2 (8.3)	1 (20.0)	0.446
Initial visual acuity (logMAR)				
Mean±SD	1.06±1.03	1.22±1.06	0.27±0.17	0.059
Median (min, max)	0.6 (0, 3)	0.77 (0.1, 3)	0.3 (0, 0.42)	0.028
Initial visual acuity (logMAR)				
20/400 or better	20 (69.0)	15 (62.5)	5 (100.0)	0.153
worse than 20/400	9 (31.0)	9 (37.5)	0	
Initial RAPD				
Positive	10 (34.5)	10 (41.7)	0	0.134
Negative	19 (65.5)	14 (58.3)	5 (100.0)	
Underlying disease				
No	18 (62.1)	13 (54.2)	5 (100)	0.158
ASCVD	9 (31.0)	9 (37.5)	0	
HIV infection	2 (6.9)	2 (8.3)	0	
Location				
Orbit	22 (75.8)	20 (83.3)	2 (40.0)	0.049
Eyelid	5 (17.2)	2 (8.3)	3 (60.0)	
Lacrimal system	1 (3.5)	1 (4.2)	0	
Eyelid and lacrimal system	1 (3.5)	1 (4.2)	0	
Ann Arbor staging				
IE & IIE	12 (41.4)	12 (50.0)	0	0.059
IIIE & IV	17 (58.6)	12 (50.0)	5 (100.0)	
Disease status at last visit				
Alive	10 (34.5)	9 (37.5)	1 (20.0)	0.633
Dead	19 (65.5)	15 (62.5)	4 (80.0)	
Treatment				
Observe	5 (17.2)	4 (16.7)	1 (20.0)	0.413
Rituximab with chemotherapy	10 (34.5)	9 (31.5)	1 (20.0)	
Chemotherapy	8 (27.5)	7 (29.2)	1 (20.0)	
Radiation	2 (6.9)	2 (8.3)	0	
Combined chemotherapy and radiation	4 (13.8)	2 (8.3)	2 (40.0)	
R-IPI				
0-2	17 (65.4)	15 (68.2)	2 (50.0)	0.519
3-5	9 (34.6)	7 (31.8)	2 (50.0)	

SD: Standard deviation; RAPD: Relative afferent pupillary defect; ASCVD: Atherosclerotic cardiovascular disease; HIV: Human immunodeficiency virus; R-IPI: Revised International Prognostic Index.

Table 2 Survival outcomes of patients with ocular adnexal diffuse large B-cell lymphoma

Clinical characteristics	*n/N*[a]	Rate/PY[b]	Median survival	cHR (95%CI)[c]	*P*
Overall	19/29	0.269	1.29	-	-
Type of lymphoma					
Primary	15/24	0.253	1.68	1	
Secondary	4/5	0.359	1.12	1.09 (0.36, 3.29)	0.883
Age at diagnosis (y)					
≤60	7/12	0.239	1.86	1	
>60	12/17	0.291	1.29	1.49 (0.59, 3.80)	0.402
Sex					
Male	7/15	0.157	1.29	1	
Female	12/14	0.461	1.29	1.73 (0.67, 4.46)	0.253
Symptom duration (d)					
≤45	12/18	0.353	1.29	1	
>45	7/11	0.192	3.16	0.88 (0.34, 2.26)	0.792
Laterality					
Unilateral	18/27	0.363	1.29	1	
Bilateral	1/2	0.048	4.42	0.32 (0.04, 2.48)	0.276
Decreased vision					
No	12/15	0.319	1.29	1	
Yes	7/14	0.213	3.16	0.61 (0.24, 1.58)	0.313
Epiphora					
No	15/25	0.220	1.86	1	
Yes	4/4	1.710	0.066	4.52 (1.38, 14.81)	0.013
Underlying disease					
No	11/18	0.180	3.15	1	
ASCVD	6/9	0.690	1.29	2.18 (0.74, 6.41)	0.155
HIV infection	2/2	2.607	0.22	8.50 (1.49, 48.47)	0.016
Disease staging					
M0	10/18	0.181	1.86	1	
M1	5/6	1.22	0.31	4.18 (1.32, 13.20)	0.015
Secondary lymphoma	4/5	0.359	1.12	1.46 (0.45, 4.67)	0.526
Ann Arbor staging					
IE & IIE	8/12	0.348	1.68	1	
IIIE & IV	11/17	0.231	1.12	0.93 (0.37, 2.32)	0.868
Tumor category					
T1-2	5/7	0.163	3.16	1	
T3-4	10/17	0.349	1.29	1.40 (0.47, 4.16)	0.541
Treatment modalities					
Without rituximab	10/14	0.280	1.29	1	0.766
With rituximab	5/10	0.403	1.86	1.04 (0.35, 3.12)	0.941
Observe	4/5	0.179	1.12	1.19 (0.37, 3.83)	
R-IPI					
0-2	10/17	0.269	1.68	1	
3-5	6/9	0.191	1.86	1.08 (0.39, 2.99)	0.885

[a]*n/N* indicates the number of events/number of eyes at risk; [b]Incidence rate is the number of events divided by total person-years (PY) at risk; [c]Crude hazard ratio (HR) for the univariate Cox proportional hazards model. ASCVD: Atherosclerotic cardiovascular disease; HIV: Human immunodeficiency virus; R-IPI: Revised-International Prognostic Index; CI: Confidence interval.

OA-DLBCL was predominant (82%), a higher proportion than that reported in a previous study from Denmark (53%)[6]. Following treatment, visual acuity (VA) outcomes for both primary and secondary OA-DLBCL patients were poorer than pre-treatment values, with mean VA of 1.72±1.10 and 0.90±1.18, respectively. The median survival was 1.68y for primary OA-DLBCL and 1.12y for secondary OA-DLBCL, with a 5-year OS rate of 27.7%. The factors significantly

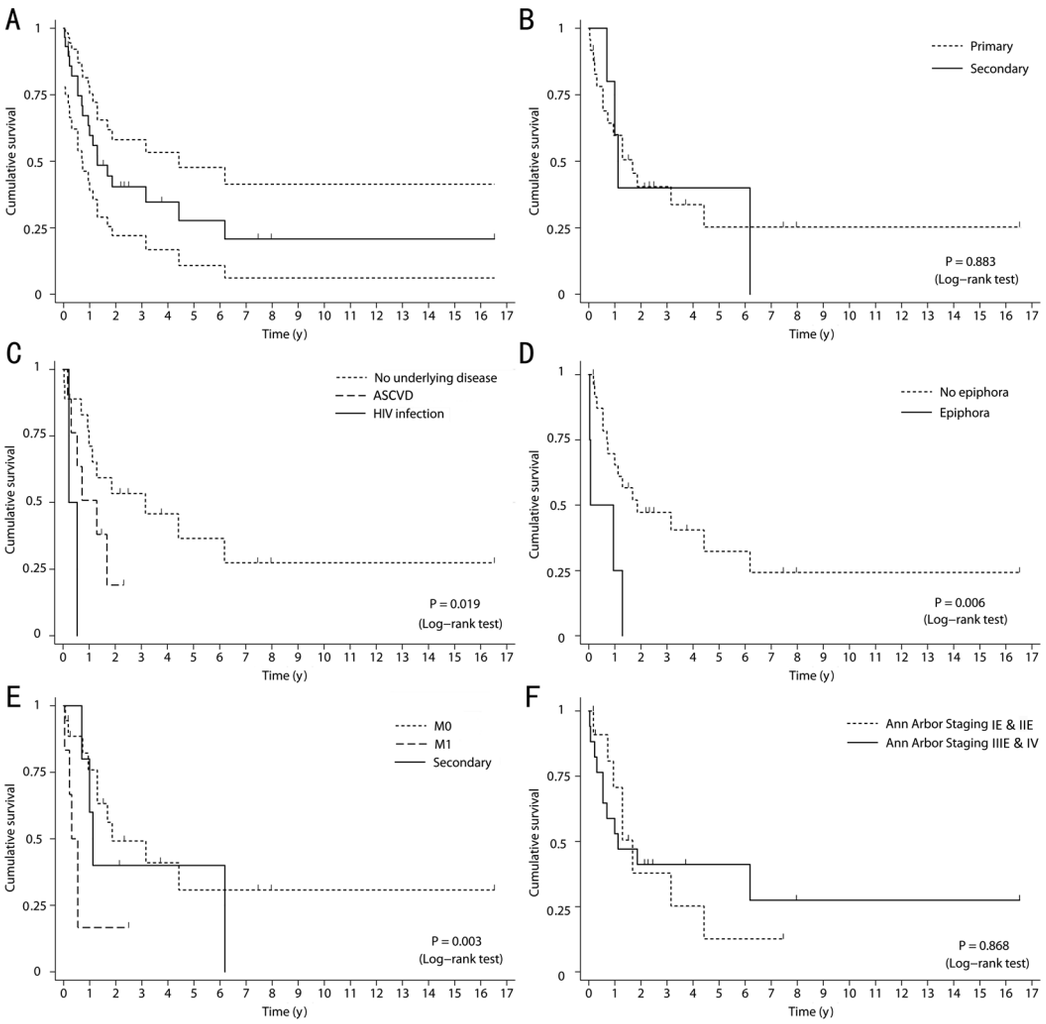

Figure 1 Kaplan-Meier Survival Curves A: Overall survival (OS) for all patients; B: OS for primary ocular adnexal diffuse large B-cell (OA-DLBCL) versus secondary OA-DLBCL; C: OS for the underlying disease; D: OS for epiphora; E: OS for the M stage at presentation; F: OS for Ann Arbor staging. ASCVD: Atherosclerotic cardiovascular disease; HIV: Human immunodeficiency virus.

Table 3 Multivariate analysis of predictive factors affecting overall survival

Clinical characteristics	Adjusted hazard ratio (95%CI)	*P* (Wald test)
Underlying disease		
No	1	
ASCVD	10.08 (1.99, 50.96)	0.005
HIV infection	12.47 (1.36, 114.04)	0.025
Epiphora		
No	1	
Yes	36.95 (5.61, 243.34)	<0.001
M staging according to TNM staging		
M0	1	
M1	6.99 (1.48, 33.06)	0.014
Secondary lymphoma	6.03 (1.24, 29.43)	0.026

ASCVD: Atherosclerotic cardiovascular disease; HIV: Human immunodeficiency virus; CI: Confidence interval.

associated with worse OS included epiphora, ASCVD, HIV infection, M1 stage, and secondary OA-DLBCL.

The median age of our cohort was 59.6y, which is lower than those reported in previous studies[6-7]. Despite this, the OS was notably poor compared to that in other studies, which reported a median OS of 42mo compared to only 15mo in our study[6] and the 5-year OS was 36.0%[6]. This discrepancy may be due to the limited access to rituximab in Thailand, where only government or state enterprise officers have free access to the medication[6]. In our study, only 34% of the patients were

treated with rituximab. Treatment modalities varied based on physician preference and patient insurance schemes, with five patients (17.2%) opting for no treatment. The OS and visual acuity of the observation group were not different from those of the treatment group because of the small number of patients in our study. Patients experienced prolonged symptom duration before hospital presentation, with half presenting within one to three months and over 20% after more than three months. This aligns with a previous finding in Southern Thailand[8].

The AJCC T staging system did not show a significant association with OS in our study, unlike larger cohort studies that found that the T category was predictive of disease-specific survival[7]. Notably, epiphora was the only symptom significantly associated with worsened OS, a novel finding in OA-DLBCL. Typically, DLBCL arising from the lacrimal sac presents as a swollen mass rather than epiphora[9]. The only other study that reported a correlation between epiphora and local relapse involved patients with extranodal marginal zone lymphoma of the ocular adnexa, likely due to the general association of epiphora with tumors of the lacrimal gland and sac[10]. In contrast, in our study, one of the four patients presenting with epiphora had a primary tumor in the lacrimal system; the others experienced ocular pain and proptosis; however, the tumor size between the epiphora and non-epiphora groups was not significantly different. We hypothesized that the epiphora resulted from keratopathy rather than obstruction of the lacrimal passage system. The staging of patients with epiphora varied: Ann Arbor stage IE, stage IIE, and stage IV, with one patient not receiving any treatment. Further studies are required to explore the association between epiphora and OS in OA-DLBCL patients.

ASCVD was also found to reduce OS significantly. Increased body mass index or visceral adipose tissue is associated with a higher relative hazard and lower estimated survival probability[11-12]. Adipose tissue affects the pharmacokinetics of drugs, including doxorubicin and rituximab, by increasing rituximab clearance and negatively impacting doxorubicin[13-14]. Patients with diabetic NHL face accelerated risks of poor survival outcomes owing to high oxidative stress, immune dysfunction, and inflammation, which affect tumorigenesis in DLBCL[15-17]. Patients with diabetes and NHL may also have a higher risk of fatal cardiovascular events, heart failure, and infection[16-17].

DLBCL is a significant acquired immune-defining cancer that is common among HIV-positive patients. In this study, HIV infection was significantly associated with poor OS. Previous studies in Thailand have indicated that HIV-positive NHL patients who do not reach the three-point National Comprehensive Cancer Network International Prognostic Index score have a poor prognosis despite antiretroviral treatment[18]. Other studies have reported a 2-year OS rate of 75% in patients with HIV-DLBCL treated with R-CHOP and antiretroviral agents[19]. Our findings are consistent with those of studies conducted in China, South Africa, and Brazil[20-23]. HIV infection affects OS through lower CD4+ cell counts and high HIV viral load titers, leading to immune deregulation, genetic alterations, and cytokine production, which promote tumor growth and progression[23-24].

In our study, analysis of AJCC staging revealed that M1 stage patients had the worst OS, with a median survival of 0.31y, paralleling studies indicating that M staging impacts progression-free survival and OS[25]. Only M staging significantly affected the OS, possibly because of the limited sample size. Analysis of Ann Arbor staging showed no significant difference between stages IE&IIE and stages IIIE&IV, suggesting that AJCC staging may be more effective in prognosticating OA-DLBCL. The Revised International Prognostic Index (R-IPI), which categorizes patients into three groups (0, very good risk; 1, 2 risk factors, good risk; and 3-5 risk factors, poor risk)[26-27] did not show a difference in OS between patients with 0-2 risk factors and those with 3-5 factors. Factors affecting OS beyond the R-IPI include underlying diseases, the presence of epiphora, and AJCC staging.

Visual outcomes also indicated a poor prognosis in patients with OA-DLBCL. Nearly half (48%) of the patients experienced visual loss at the last follow-up, with a mean VA of 1.57±1.14. The causes of VA deterioration include compressive optic neuropathy, exposure to keratitis, and glaucoma. A previous study reported reduced vision in 20% of the patients, all of whom had compressive optic neuropathy with a positive relative afferent pupillary defect[28]. Limited research exists on the visual prognosis of OA-DLBCL, and our findings suggest the importance of early tissue diagnosis and prompt treatment to prevent visual deterioration and improve patient quality of life.

This retrospective investigation spanned nearly two decades in southern Thailand. Despite its longevity, this study had limitations, including incomplete data entries, missing data, and selection bias. The sample size was also limited, owing to the rarity of the disease, particularly in the ocular adnexal regions. Consequently, although this study offers valuable insights, its statistical power may be compromised. Future studies should include nationwide investigations, larger patient cohorts, and more prospective studies.

In conclusion, half of the patients with primary OA-DLBCL had advanced disease according to the Ann Arbor stage, predominantly T4 disease. Factors such as epiphora, ASCVD, HIV infection, M1 category, and secondary lymphoma are associated with poor OS in patients with OA-DLBCL. Visual

prognosis and OS demonstrated unfavorable results despite treatment.

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