# Non-specific orbital inflammation: Clinical and histopathological insights from a 6-year single-centre Malaysian cohort

**Sharifah Izzati Sayed Jamaludin, MD[1,2], Muhammad Farez Mukhriz Jefridin, MBBS[1], Adlina Abdul Rahim, MMed[1], Muzaliha Mohamed Nor, MMed[1], Shahidatul Adha Mohamad, MMed[2]**

[1]Department of Ophthalmology, Hospital Sultanah Bahiyah, Alor Setar, Kedah, Malaysia, [2]Department of Ophthalmology and Visual Science, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia.

## ABSTRACT

**Introduction: Non-specific orbital inflammation (NSOI), formerly known as idiopathic orbital inflammatory disease (IOID), is a rare, exclusion-based orbital disorder with diverse clinical manifestations. This study evaluates the demographic patterns, clinical features, histopathological profiles, and treatment outcomes of NSOI cases managed at a tertiary referral centre in Malaysia.**

**Materials and Methods: A six-year retrospective review was conducted at a tertiary referral centre in northern Malaysia, involving 36 patients diagnosed with NSOI between January 2018 and December 2023. Diagnosis was based on clinical features, exclusion of systemic and infectious causes through serology, and supportive imaging or biopsy findings. Only cases with histopathological confirmation and immunohistochemical staining negative for lymphoma, carcinoma, and other malignancies were included. Data included demographics, clinical presentation, imaging and histopathological findings, serologic evaluations, and treatment modalities. Outcomes were assessed based on symptom resolution, radiologic improvement, recurrence, and treatment response.**

**Results: Most patients were male (61.1%), with a mean age of 43.6 years. Unilateral involvement predominated (77.8%). Common presentations included periorbital swelling (69.4%), ophthalmoplegia (22.2%), conjunctival mass (22.2%), and proptosis (19.4%). Imaging revealed frequent involvement of the lacrimal gland (45.8%), extraocular muscles (37.5%), and conjunctiva (37.5%). The main histopathological findings included reactive lymphoid hyperplasia (40%), granulomatous inflammation (20%), and chronic inflammation (23.3%). Of the 36 patients, 19 received medical treatment, with 84.2% given systemic corticosteroids, while the remaining 17 patients were managed conservatively without any medical treatment, and they remained clinically stable throughout follow-up with no evidence of disease progression. Among treated cases, recurrence occurred in 25%, predominantly in males.**

**Conclusion: NSOI shows varied clinical and anatomical patterns. Corticosteroids remain the mainstay of treatment, but conservative management is appropriate in stable, non-progressive cases when close monitoring and diagnostic exclusion are assured. These findings support individualised therapeutic strategies and long-term follow-up.**

**KEYWORDS:**
*Non-specific orbital inflammation, orbital pseudotumor, idiopathic orbital inflammation, IOID, myositis*

## INTRODUCTION

Non-specific orbital inflammation (NSOI), previously referred to as idiopathic orbital inflammatory disease (IOID) or orbital pseudotumor, is a non-infectious, exclusion-based inflammatory disorder of the orbit.[1] It ranks the third most common orbital inflammatory condition after thyroid eye disease and orbital lymphoma.[1,2] Although considered benign, NSOI poses diagnostic and therapeutic challenges due to its variable presentation and overlap with other orbital pathologies.[3]

NSOI may involve a wide range of orbital tissues, including the lacrimal gland, extraocular muscles, conjunctiva, optic nerve sheath, and orbital fat.[1,2] Imaging, particularly magnetic resonance imaging (MRI), is essential for assessing disease extent and excluding mimickers.[4] Histopathological evaluation (HPE), while not routinely performed, plays a pivotal role in confirming diagnosis and subclassifying inflammation, especially in cases of recurrence, steroid-refractory disease, or diagnostic uncertainty.[1,3,5]

Systemic corticosteroids remain the cornerstone of treatment, with close observation considered in patients with stable, non-vision-threatening disease.[1,6] Despite its clinical relevance, data on NSOI from Southeast Asia remain limited. This study characterises the clinical spectrum, diagnostic strategies, and treatment outcomes of NSOI at a Malaysian tertiary referral centre.

## MATERIALS AND METHODS

This retrospective study analysed 36 patients diagnosed with NSOI at the Oculoplastic Clinic of Hospital Sultanah Bahiyah, a tertiary referral centre serving northern Peninsular Malaysia, between January 2018 and December 2023. The diagnosis was established through clinical

*This article was accepted: 4 February 2026*
*Corresponding Author: Shahidatul-Adha Mohamad*
*Email: shieda@usm.my*

assessment, serological exclusion of systemic and infectious aetiologies, and corroborative imaging or biopsy findings. Only patients with HPE and immunohistochemical staining negative for lymphoma, carcinoma, and other malignancies were included. The study was approved by the hospital administration and conducted in accordance with the Declaration of Helsinki. Informed written consent was obtained from all participants.

Medical records were reviewed to extract demographic data, clinical features, imaging and histopathological findings (where available), serologic test results for systemic and infectious mimickers, treatment modalities, and clinical outcomes. Patients were stratified by disease course into acute (< 2 weeks), subacute (2-6 weeks), and chronic (> 6 weeks) groups. NSOI was further classified by anatomical involvement (e.g., lacrimal gland, extraocular muscles, orbital fat, conjunctiva) and orbital location (anterior, diffuse, posterior, apical) based on imaging and HPE. Descriptive statistics were used to summarise demographic data, clinical characteristics, imaging findings and treatment outcomes.

## RESULTS

Most of the confirmed NSOI patients enrolled in this study were males (61.1%), with a mean age of 43.61 ± 15.39 years. Eight patients had bilateral eye involvement. Most patients had a chronic disease course, presenting with symptoms lasting more than 6 weeks. Periorbital swelling was the most common presenting complaint, while conjunctival injection, eye pain, and diplopia were reported less frequently (Table I). Visual acuity remained unaffected in all patients, with no reported cases of vision loss. The most common features observed at presentation were ophthalmoplegia (22.2%), conjunctival mass (22.2%), and proptosis (19.4%).

The categorisation of NSOI cases in this study was based on the anatomical structures affected, as determined by imaging, and the pathological processes identified through HPE. Imaging studies were performed in 24 patients, with the majority undergoing computed tomography (CT) and one undergoing MRI, while biopsies were conducted in 30 patients. The most involved structures on imaging were the lacrimal gland (45.8%), extraocular muscles (37.5%), and conjunctiva (37.5%). Among the anatomical subtypes observed, anterior involvement predominated, as detailed in Table II. HPE revealed microscopic features of lymphoid hyperplasia in over half of the cases (53.4%), compared to granulomatous inflammation in 20% of cases (Table III). IgG4 immunostaining was performed in two biopsied cases, both of which were negative.

Of the 36 patients, 19 received medical treatment, while 17 were managed conservatively with close observation and no active medical therapy. Systemic corticosteroids were the first-line treatment in the majority of treated patients (84.2%). Oral prednisolone was initiated at 0.5-1 mg/kg/day (maximum 80 mg) and tapered weekly by 5-10 mg, with adjustments based on clinical response. In selected cases with more extensive orbital or optic nerve involvement, intravenous methylprednisolone (1 g/day for 3 consecutive days) was administered at presentation, followed by oral prednisolone 1 mg/kg/day with a similar tapering regimen. Topical corticosteroids were prescribed for patients with localised conjunctival masses. Due to concerns regarding psychiatric comorbidity, one patient received non-steroidal anti-inflammatory therapy instead of systemic corticosteroids.

In steroid-refractory cases or those with disease recurrence, steroid-sparing immunomodulatory therapy was initiated, including methotrexate (starting at 15 mg weekly), azathioprine (starting at 150 mg daily), or a combination of both, with doses adjusted according to clinical response. One patient with perineural optic nerve involvement extending to the orbital apex showed a suboptimal response despite prolonged corticosteroid therapy and required the addition of methotrexate. Two other patients with extensive orbital and bilateral lacrimal gland involvement experienced recurrence after an initial remission and were subsequently treated with azathioprine and methotrexate, respectively.

In contrast, those treated conservatively comprised patients with small, stable eyelid masses, chronic lid swelling or proptosis persisting for months to years without redness, pain, or visual impairment. All remained clinically stable or slightly improved over the observation period, without evidence of progression.

## DISCUSSION

NSOI is a diagnosis of exclusion, characterised by idiopathic inflammation of orbital tissues in the absence of systemic or infectious causes.[2,6-8] This retrospective series represents the most detailed characterisation of NSOI in Malaysia to date and contributes valuable data from Southeast Asia, where published literature remains limited. Unlike most Western and regional reports that describe a female predominance in the fifth decade of life,[1,2,9,10] our cohort was predominantly male, with a younger mean age of 43.6 years. Notably, two paediatric cases (ages 8 and 12) were identified, highlighting the need to consider NSOI in children and adolescents. Although rare, paediatric presentations have been reported, with variable features ranging from isolated orbital inflammation to systemic overlap syndromes.[11,12]

Consistent with existing literature, our cohort demonstrated predominantly unilateral cases and a wide spectrum of clinical manifestations. The lacrimal gland was the most involved structure, aligning with prior reports of dacryoadenitis-type NSOI as a common presentation.[10,13,14] Conjunctival and extraocular muscle involvement were equally prevalent, further highlighting the anatomical heterogeneity and diagnostic complexity of the condition.[9] Although all patients maintained good visual acuity, two were radiologically diagnosed with optic neuritis and optic perineuritis, underscoring the need for comprehensive optic nerve function testing beyond Snellen acuity. The presence of ophthalmoplegia despite otherwise normal anterior segment and fundus examinations reinforces the importance of thorough clinical and radiologic evaluation to exclude mimickers such as thyroid eye disease, cranial nerve palsies, orbital apex syndrome, and cavernous sinus or brainstem pathology.[3,4,6,7,15]

**Table I: Demographic profile and clinical characteristics of NSOI (n = 36)**

| Variables | n (%) |
|---|---|
| Age (years) | |
| Mean ± SD: 43.61 ± 15.39 (range: 8-71) | |
| Gender | |
| Male | 22 (61.1) |
| Female | 14 (38.9) |
| Race | |
| Malay | 28 (77.8) |
| Chinese | 5 (13.9) |
| Indian | 3 (8.3) |
| Disease Course | |
| Acute | 8 (22.2) |
| Subacute | 4 (11.1) |
| Chronic | 24 (66.7) |
| Laterality | |
| Unilateral | 28 (77.8) |
| Bilateral | 8 (22.2) |
| Presenting Symptoms | |
| Periorbital swelling | 18 (50.0) |
| Conjunctival injection | 4 (11.1) |
| Eye pain | 3 (8.3) |
| Diplopia | 3 (8.3) |
| Clinical Signs at Presentation | |
| Ophthalmoplegia | 8 (22.2) |
| Conjunctival mass | 8 (22.2) |
| Proptosis | 7 (19.4) |
| Optic neuropathy (RAPD) | 1 (2.8) |
| Chemosis | 2 (5.6) |
| Palpable periorbital mass | 2 (5.6) |
| Ptosis | 1 (2.8) |
| Treatment | |
| Yes | 19 (52.8) |
| Systemic corticosteroid | 16 (84.2) |
| - Oral corticosteroid (initial treatment) | 14 (73.7) |
| - Intravenous corticosteroid (initial treatment) | 2 (10.5) |
| Topical corticosteroid | 2 (10.5) |
| Immunomodulators | 3 (15.8) |
| NSAIDS | 1 (5.3) |
| No (Observation only) | 17 (47.2) |
| Recurrence | |
| Treated group | 9 (47.4) |
| Non-treated group | - |

RAPD, relative afferent pupillary defect; NSAID, non-steroidal anti-inflammatory drug

**Table II. Imaging-based characteristic of NSOI (n = 24)**

| Subtype of NSOI | n (%) |
|---|---|
| Tissue-specific subtype | |
| Lacrimal gland (Dacryoadenitis) | 11 (45.8 |
| Extraocular muscles (Myositis) | 9 (37.5) |
| Optic nerve (Optic Neuritis) | 1 (4.2) |
| Optic nerve sheath (Optic Perineuritis) | 1 (4.2) |
| Orbital mass | 3 (12.5) |
| Orbital fat | 1 (4.2) |
| Conjunctiva | 9 (37.5) |
| Eyelid | 4 (16.7) |
| Lacrimal sac and duct | 2 (8.3) |
| Anatomical subtype | |
| Anterior | 18 (75.0) |
| Diffuse | 4 (16.7) |
| Posterior | 1 (4.2) |
| Apical | 1 (4.2) |
| Dacryoadenitis | 7 (29.2) |
| Myositis | 5 (20.8) |

**Table III: Histopathological features observed in NSOI cases (n=30)**

| Histopathological Features | n (%) |
|---|---|
| Reactive lymphoid hyperplasia | 12 (40.0) |
| Benign lymphoid hyperplasia | 4 (13.4) |
| Granulomatous inflammation | 6 (20.0) |
| Chronic inflammation | 7 (23.3) |
| No obvious inflammation | 1 (3.3) |

Imaging is the cornerstone of NSOI diagnosis,16 particularly in our patients who declined biopsy due to concerns about surgical procedures and operative risks. CT was the primary modality used, given its accessibility and ability to delineate anatomical involvement, supporting diagnosis in cases where histopathological confirmation was not feasible. MRI offers superior soft tissue contrast and is especially useful for evaluating optic nerve involvement, orbital apex pathology, and intracranial extension,[4,16] but was not routinely performed due to cost and availability constraints.

Excluding infectious, autoimmune, and systemic causes is essential before diagnosing NSOI, given its nature as a diagnosis of exclusion.[3,5-7,17] However, the definitive diagnosis often relies on HPE analysis, especially when clinical and imaging findings are inconclusive.[1,2,15] Lymphoid hyperplasia was the predominant finding in our cohort, with reactive subtypes more common than benign forms. While both reflect lymphoid proliferation, reactive hyperplasia typically indicates a polyclonal inflammatory response, whereas benign hyperplasia may show organised follicular architecture, occasionally mimicking low-grade lymphoma.18 Granulomatous and chronic inflammation were also observed. The latter referred to non-specific infiltrates lacking defining features, possibly representing early-stage disease, treated lesions, or diagnostically indeterminate inflammation.[1]

Recent literature suggests that up to 50% of biopsy-proven NSOI cases may represent IgG4-related orbital disease (IgG4-ROD), a distinct clinicopathological entity with systemic implications. Despite increasing global recognition, reported cases from Malaysia remain limited, with the first case published in 2018 and only a few subsequent reports. This scarcity may reflect underdiagnosis, restricted access to IgG4 testing, or a genuinely lower local prevalence. In Malaysia, the diagnosis of IgG4-ROD is often hindered by broader healthcare resource limitations, while definitive confirmation remains further challenged by the restricted availability and high cost of histopathology and IgG4-specific immunohistochemistry services. In the absence of routine testing and comprehensive epidemiological data, the true burden remains uncertain. Future studies incorporating standardised immunohistochemistry are warranted to enable accurate subclassification of NSOI and guide long-term management strategies.

Management of NSOI is progressively expanding beyond corticosteroids to incorporate anti-metabolites (e.g., methotrexate, azathioprine), biologic and molecular therapies (including rituximab, TNF-α inhibitors, and IL-6 blockade) and emerging small-molecule treatments such as JAK inhibitors.1 While these approaches reflect a shift toward more targeted therapy, their use remains largely off-label and is supported primarily by limited observational data.[1]

In our cohort, systemic corticosteroids remained the first-line therapy, consistent with established treatment paradigms for NSOI.[3,5,6,21] Immunomodulatory agents, particularly azathioprine and methotrexate, were used in steroid-refractory cases, as previously reported, particularly those with dacryoadenitis, myositis, or perineuritis—subtypes frequently associated with recurrence.[3,5,7,21] Notably, findings from a French cohort report suggest that a cellular histological pattern and orbital fat involvement may be risk factors for corticosteroid failure, even in patients receiving high-dose therapy.[22] These features were observed in some of our refractory cases, supporting the need for early identification of high-risk patterns to guide escalation of immunosuppression. Although less commonly used, biologic agents, low-dose orbital radiotherapy, and surgical intervention remain potential options for refractory disease.[1,3,23]

Nearly half of our patients were managed conservatively due to indolent non-progressive disease, supported by negative serologic investigations and absence of visual disturbances. Their clinical phenotype, small lid mass or chronic, painless lid swelling or proptosis persisting for months to years without visual compromise or inflammatory signs, likely represents a less aggressive variant of idiopathic orbital inflammatory disease, typically involving anterior or localised regions with minimal functional impairment and no optic nerve involvement. This observation supports prior reports suggesting that NSOI may be self-limiting in selected cases.[24] However, conservative management should only be considered when imaging or biopsy excludes serious pathology, serologic screening is negative, and close follow-up is feasible. Identifying predictors of indolent NSOI, such as anatomical subtype, disease duration, and inflammatory markers, remains an important area for future research.

## CONCLUSION

This study reinforces the broad clinical spectrum and heterogeneity of NSOI. While corticosteroid therapy remains the mainstay of treatment, not all patients achieve complete resolution, and some experience recurrence or persistent low-grade inflammation. Indolent cases may remain stable without intervention, suggesting that observation is reasonable when diagnostic confidence is high and follow-up is assured. Future studies should aim to identify predictors of disease activity, treatment response, and recurrence to optimise individualised management strategies.

## REFERENCES


1. Wu KY, Kulbay M, Daigle P, Nguyen BH, Tran SD. Nonspecific orbital inflammation (NSOI): unraveling the molecular pathogenesis, diagnostic modalities, and therapeutic interventions. Int J Mol Sci 2024; 25(3): 1553.
2. Lee MJ, Planck SR, Choi D, Harrington CA, Wilson DJ, Dailey RA et al. Non-specific orbital inflammation: current understanding and unmet needs. Prog Retin Eye Res 2021; 81: 100885.
3. Shao Y, Ma JM, Yang HS. Guidelines for the standardized diagnosis and treatment of non-specific orbital inflammation (2024). Int J Ophthalmol 2024; 17(12): 2203-13.
4. Ang T, Tong JY, Patel S, Selva D. Differentiation of bacterial orbital cellulitis and diffuse non-specific orbital inflammation on magnetic resonance imaging. Eur J Ophthalmol 2025; 35(2): 727-33.
5. Yeşiltaş YS, Gündüz AK. Idiopathic orbital inflammation: review of literature and new advances. Middle East Afr J Ophthalmol 2018; 25(2): 71.
6. Fang Y, Shen B, Dai Q, Xie Q, Wu W, Wang M. Orbital inflammatory pseudotumor: new advances in diagnosis, pathogenesis, and treatment. Eur J Med Res 2023; 28(1): 395.
7. Ang T, Juniat V, Shapira Y, Selva D. Systemic inflammatory markers differentiate between orbital cellulitis and non-specific orbital inflammation. Orbit 2023; 42(3): 245-50.
8. Enghelberg M, Go J, Adika A, Sanchez-Gonzalez MA, Georgescu D, Kay M. Non-specific orbital inflammation and sclerosing variant. Pan-Am J Ophthalmol 2017; 16(4): 103-9.
9. Eshraghi B, Sonbolestan SA, Abtahi MA, Mirmohammadsadeghi A. Clinical characteristics, histopathology, and treatment outcomes in adult and pediatric patients with nonspecific orbital inflammation. J Curr Ophthalmol 2019; 31(3): 327-34.
10. Andrew NH, Kearney D, Sladden N, McKelvie P, Wu A, Sun MT et al. Idiopathic dacryoadenitis: clinical features, histopathology, and treatment outcomes. Am J Ophthalmol 2016; 163: 148-53.
11. Uddin JM, Rennie CA, Moore AT. Bilateral non-specific orbital inflammation (orbital "pseudotumour"), posterior scleritis, and anterior uveitis associated with hypothyroidism in a child. Br J Ophthalmol 2002; 86(8): 936.
12. Elashmawy A, Stephan C, Shetty A, Yangouyian A, Sharif S, Yangouy A. Idiopathic orbital inflammatory disease in a pediatric patient: a case report highlighting the diagnostic reasoning and treatment strategy. Cureus 2024; 16(8): e67569.
13. Yuen SJA, Rubin PA. Idiopathic orbital inflammation. Arch Ophthalmol 2003; 121(4): 491-9.
14. Mombaerts I. The many facets of dacryoadenitis. Curr Opin Ophthalmol 2015; 26(5): 399-407.
15. Young SM, Chan AS, Al Jajeh I, Shen S, Seah LL, Choo CT et al. Clinical features and treatment outcomes of orbital inflammatory disease in Singapore: a 10-year clinicopathologic review. Ophthalmic Plast Reconstr Surg 2017; 33(3): 182-8.
16. Yoon MK, Lu JE. An evidence-based approach to diagnosing patients presenting with orbital inflammatory syndromes (an American Ophthalmological Society Thesis). Am J Ophthalmol 2024; 266: 156-81.
17. Gülle S, Durmaz Engin C, Özizmirliler D, Men S, Önen F, Söylev Bajin M. Orbital inflammatory disease: a joint clinical experience in rheumatology and ophthalmology. Int Ophthalmol 2025; 45(1): 48.
18. Segura-Rivera R, Marques-Piubelli ML, Miranda RN. Reactive B cell rich lymphoid proliferations that can mimic lymphoma. PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/lymphnodesreactivebcellrichlymphprolif.html. Accessed November 4th, 2025.
19. Aryasit O, Tiraset N, Preechawai P, Kayasut K, Sanghan N, Sittivarakul W. IgG4-related disease in patients with idiopathic orbital inflammation. BMC Ophthalmol 2021; 21(1): 356.
20. Azman SA, Omar N, Bahari N, Hussin H. Worsening proptosis: diffuse large B-Cell lymphoma associated with chronic inflammation arising within IgG4-related orbital disease. Malays J Med Health Sci 2021; 17.
21. Al-Ghazzawi K, Neumann I, Knetsch M, Chen Y, Wilde B, Bechrakis NE et al. Treatment outcomes of patients with orbital inflammatory diseases: should steroids still be the first choice? J Clin Med 2024; 13(14): 3998.
22. La Rosa A, Groh M, Martin A, Ba ST, Cucherousset N, Mouriaux F et al. Cellular pattern and orbital fat involvement are possible risk factors for the failure of corticosteroids in patients with pure idiopathic orbital inflammation syndrome: lessons from the French prospective SIOI cohort study (part II). BMJ Open Ophthalmol 2024; 9(1).
23. Zuraski C, Yoon JS, Lieu AC, Topilow N, Pizzo D, Korn BS, et al. Periostin: a promising biomarker in nonspecific orbital inflammation and orbit-involving IgG4 disease. Orbit 2025:1-8.
24. Chirapapaisan N, Chuenkongkaew W, Pornpanich K, Vangveeravong S. Orbital pseudotumor: clinical features and outcomes. Asian Pac J Allergy Immunol 2007; 25(4): 215.