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HEAD AND NECK IMAGING

ORIGINAL ARTICLE

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T2 signal ratio enhances the diagnostic performance of apparent diffusion coefficient in differentiating orbital lymphoma from inflammatory mimickers

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PURPOSE

Orbital lymphomas share overlapping clinical and radiological features with immunoglobulin G4-related orbital disease (IgG4-ROD) and granulomatous orbital diseases, which may lead to diagnostic delays. This study aims to evaluate the added diagnostic value of the transverse relaxation time (T2) signal ratio when combined with apparent diffusion coefficient (ADC) measurements in distinguishing orbital lymphoma from inflammatory mimickers.

METHODS

In this retrospective study, two blinded radiologists independently measured T2 signal ratios (lesion to cerebral cortex), ADC values, and ADC ratios on pretreatment orbital magnetic resonance imaging scans of 58 patients (21 lymphomas, 21 IgG4-ROD, 16 granulomatous inflammation). Measurements were performed on axial images at the lesion's maximal diameter. Regions of interest were manually drawn to cover the entire lesion, avoiding necrosis and edges. Diagnostic performance was assessed using receiver operating characteristic curve analysis, with optimal cut-off values determined by Youden's index. The ADC ratio (≤1) and T2 signal ratio (>0.88) were combined using OR (either positive) and AND (both positive) rules. Interobserver agreement was evaluated using intraclass correlation coefficients (ICC).

RESULTS

All measurements showed statistically significant differences between the two cohorts. Reviewer 1's ADC ratio measurements demonstrated excellent diagnostic performance, with an area under the curve (AUC) of 0.920 (85.7% sensitivity and 86.5% specificity at the optimal cut-off of ≤1). In comparison, T2 signal ratios showed moderate diagnostic value (AUC: 0.726; 80.95% sensitivity and 64.86% specificity at a cut-off >0.88). The combination of both parameters significantly improved diagnostic accuracy: the OR rule (ADC ≤1 or T2 >0.88) increased sensitivity to 95.2%, whereas the AND rule (ADC ≤1 and T2 >0.88) increased specificity to 94.6%. Interobserver reliability was excellent, with ICC values ranging from 0.969 to 0.985.

CONCLUSION

Although diffusion imaging remains the primary discriminator for orbital lymphoma, the T2 signal ratio considerably enhances diagnostic confidence, particularly in borderline ADC cases.

CLINICAL SIGNIFICANCE

Incorporating T2 signal ratio measurements adds minimal workflow burden in routine clinical practice and provides a practical tool for differentiating lymphoma from IgG4-ROD and granulomatous inflammatory mimics.

KEYWORDS

Granulomatous inflammation, immunoglobulin G4-related disease, lymphoma, magnetic resonance imaging, orbit

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Orbital lymphoma is the most common orbital neoplasm in adults, with extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) being the most frequent histopathological subtype.[1] Differentiating orbital lymphoma from inflammatory mimickers is crucial because treatment implications and prognosis differ. Orbital lymphomas are primarily treated with low-dose radiotherapy (20–30 Gy), whereas combined-modality therapy with systemic agents (e.g., rituximab or chemotherapy) is required for aggressive subtypes. In contrast, inflammatory conditions [e.g., immunoglobulin G4-related orbital disease (IgG4-ROD)] often respond well to corticosteroid therapy.[2,3]

Clinical manifestations are largely non-discriminating, and intraorbital location may interfere with obtaining adequate tissue samples for histopathologic evaluation. Magnetic resonance imaging (MRI) has an established role in preoperative discrimination. Several prior studies have reported descriptive and quantitative MRI features for differentiating orbital lymphoma from inflammatory diseases, including margin characteristics, diffusion, and perfusion patterns.[3-6] Nevertheless, studies comparing lymphoma with specific entities of orbital inflammation remain sparse.[7]

Orbital inflammation is an umbrella term that includes idiopathic orbital inflammation (IOI) and specific entities with established diagnostic criteria, such as IgG4-ROD. IOI can be more readily differentiated from orbital lymphoma both clinically and radiologically, as it typically presents with pain and demonstrates an infiltrative pattern without restricted diffusion.[8] However, IgG4-ROD and granulomatous orbital inflammation share overlapping clinical and radiological features with lymphoma, such as mass-like involvement and relatively low apparent diffusion coefficient (ADC) values.[9-11] Therefore, the role of diffusion-weighted imaging (DWI) in distinguishing orbital lymphoma from these specific inflammatory entities may be limited, necessitating additional imaging discriminators.

IgG4-ROD and granulomatous inflammations usually appear hypointense on transverse relaxation time (T2)-weighted images due to fibrosis and granulomas, respectively.[12] In contrast, orbital lymphomas have mostly been reported to demonstrate iso- or hyperintense T2 signals in previous studies.[1,13] Thus, T2 signal intensity may serve as a useful discriminator between orbital lymphoma and these inflammatory entities.

In this study, we aim to retrospectively assess the diagnostic performance of ADC values, T2 signal intensity measurements, and their combination in differentiating orbital lymphoma from its most challenging mimickers: IgG4-ROD and granulomatous diseases.

Main points

- Apparent diffusion coefficient (ADC) values demonstrate superior diagnostic performance for lymphoma detection, but the overlap with immunoglobulin G4-related orbital disease (IgG4-ROD) and granulomatous diseases necessitates additional imaging markers.
- Transverse relaxation time (T2) hypointensity in IgG4-ROD and granulomatous diseases versus intermediate T2 signal intensity in lymphomas provides complementary diagnostic value when ADC findings are equivocal.
- The combined ADC and T2 approach relies on routine magnetic resonance imaging sequences without requiring advanced protocols, offering a clinically practical solution to guide treatment decisions.

Methods

Patients

This retrospective study was conducted with approval from the Hacettepe University Health Sciences Research Ethics Board, with a waiver of informed consent (SBA 24/1115/2024, date: 27.11.2024). Orbital MRI reports dictated in the radiology department between January 2016 and January 2024 were searched for the keywords "lymphoma," "intraorbital mass," "inflammation," and "granulomatous". An additional retrospective search was conducted in the rheumatology department database to identify patients diagnosed with orbital IgG4-ROD, granulomatous polyangiitis (GPA), or sarcoidosis.

The inclusion criteria were as follows: 1) patients with an orbital mass or infiltration detected by MRI; 2) patients meeting established diagnostic criteria and/or having a histopathologic diagnosis of IgG4-related disease[14] or granulomatous diseases, including GPA[15] and sarcoidosis;[16] 3) patients with a histopathologic diagnosis of orbital lymphoma; 4) patients who underwent orbital MRI at the onset of orbital disease. A total of 36 patients with orbital lymphoma, 26 patients with IgG4-ROD, 10 patients with GPA, 5 patients with sarcoidosis, and 1 patient with fungal granulomatous angiitis were identified.

The exclusion criteria were as follows: 1) MRI performed after biopsy and/or corticosteroid use, 2) secondary orbital lymphoma, 3) technically inadequate scans, and 4) scans without DWI. A total of 15 patients with orbital lymphoma (14 with secondary lymphoma, 1 with a technically inadequate scan) and 5 patients with IgG4-ROD (3 without DWI, 1 with corticosteroid use, 1 with a technically inadequate scan) were excluded. The final study group (Figure 1) comprised 21 patients with primary orbital lymphoma (9 women and 12 men; age range 9-86 years;

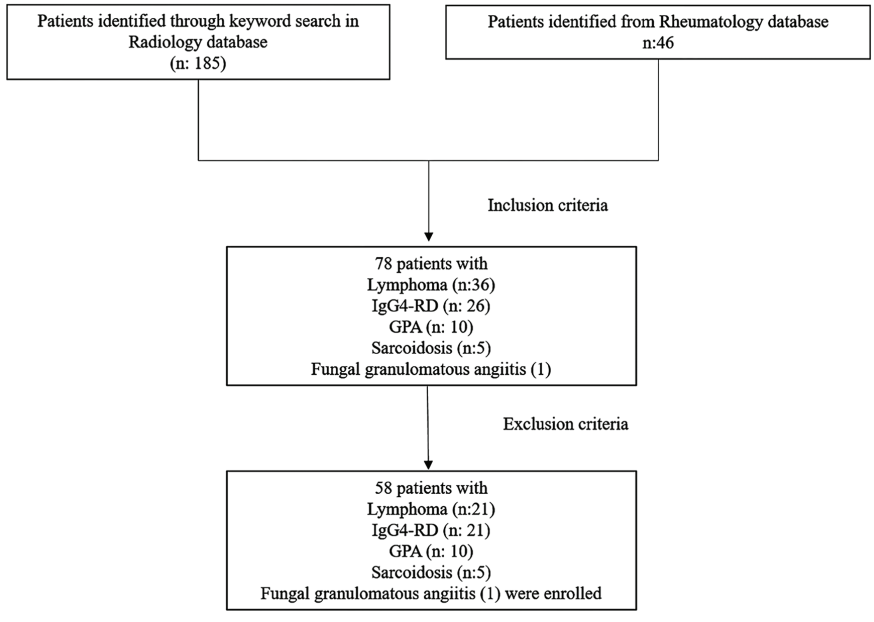

Figure 1. Flowchart of patient selection. IgG4-ROD, immunoglobulin G4-related orbital disease; GPA, granulomatous polyangiitis.

median 58.4 years), 21 patients with IgG4-ROD (13 women and 8 men; age range 4-65 years; median 37 years), 10 patients with orbital GPA (7 women and 3 men; age range 11-64 years; median 41.5 years), 5 patients with sarcoidosis (5 women; age range 26-59 years; median 44 years), and 1 patient with fungal granulomatous angiitis (78-year-old woman).

Magnetic resonance imaging examination

MR studies were performed using either 1.5 T or 3 T MR scanners (Philips Healthcare, Best, the Netherlands; GE Healthcare, Milwaukee, WI, USA; and Siemens, Erlangen, Germany). The orbital MRI protocol included coronal and axial T1-weighted images, coronal and axial T2-weighted images with fat saturation, post-contrast axial and coronal T1-weighted images with fat saturation, and axial DWI.

The parameters for fat-saturated T2-weighted images were as follows: repetition time (TR)/echo time (TE): 5,680–2,720/100–80 ms, field of view (FOV): 215 × 215–120 × 105 mm, slice thickness/gap: 3–4/3.3–4.6 mm, number of excitations (NEX): 2–3, and matrix: 320 × 302–612 × 768. DWI was acquired using single-shot spin-echo echo planar imaging with the following parameters: TR/TE: 6,188–2,400/116–73 ms; slice thickness: 3–5 mm; flip angle: 90°; FOV: 267 × 227–160 × 100 mm; NEX: 2–12; matrix 256 × 256–128 × 128; and b values of 0 and 1,000 sec/mm^2.

Image analysis

The images were reviewed by two head and neck radiologists (Reviewer 1 and Reviewer 2, with 11 and 7 years of experience, respectively), both blinded to the clinical diagnosis. Descriptive features, including laterality and location, were assessed by consensus. When both sides were affected, the larger area of involvement was selected for quantitative analysis. Quantitative analysis included T2 signal and ADC measurements. Measurements were made independently on axial planes at the level of maximal lesion diameter. Regions of interest (ROIs) were drawn manually to cover the entire lesion, avoiding cystic or necrotic areas by referencing post-contrast T1-weighted images. Lesion edges were excluded to reduce the effects of partial volume and susceptibility artifacts. The mean ROI sizes drawn by Reviewers 1 and 2 were as follows: for Reviewer 1, the T2 signal ROI was 2.62 cm^2 (range: 0.3–9.38 cm^2), and the ADC ROI was 2.56 cm^2 (range: 0.16–9.32 cm^2). For Reviewer 2, the T2 signal ROI was 2.08 cm^2 (range: 0.25–7.36 cm^2), and the ADC ROI was 1.84 cm^2 (range: 0.23–5.81 cm^2).

The ratios of T2 signal (lesion to mean T2 signal cortex) and ADC (lesion to mean ADC cortex) were calculated for each patient. The mean T2 signal cortex and ADC cortex values were derived from three separate cerebral cortical measurements taken on the same axial plane where lesion T2 signal and ADC values were measured. For cortical reference values, three circular ROIs (0.04–0.15 cm^2) were placed in areas with optimal gray–white matter differentiation, carefully avoiding white matter and sulci (Figure 2).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 23.0 (IBM Corp., Armonk, NY, USA). Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. The Kolmogorov–Smirnov test was used to assess the normality of continuous variables. Normally distributed variables were presented as mean ± standard deviation, and group comparisons were made using independent samples t-tests. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of T2 signal ratios and ADC values/ratios in differentiating orbital lymphoma from orbital inflammation. Optimal cut-off values were determined using the Youden index, an objective criterion that balances diagnostic test performance by identifying the threshold that maximizes both sensitivity and specificity simultaneously, corresponding to the point on the ROC curve nearest the upper-left corner (representing perfect discrimination). Based on these cut-off points, the two variables were converted into binary outcomes and combined using: (1) the "OR rule" (positive if either parameter was positive) and (2) the "AND rule" (positive only if both parameters were positive). The sensitivity and specificity of each combined test were calculated. Inter-rater reliability was assessed using intraclass correlation coefficients (ICC). A P value of <0.05 was considered statistically significant.

Findings

A total of 86% of patients with primary orbital lymphoma had low-grade non-Hodgkin lymphoma, and MALT lymphoma constituted 57% of all cases. The mean age of patients with lymphoma (58.48 ± 21.18 years) was higher than that of patients with orbital inflammatory diseases (40.54 ± 19.06 years) (P = 0.002). No significant difference in gender distribution was observed between the lymphoma and inflammatory cohorts. Comparative analyses of descriptive findings are presented in Table 1. The majority of patients with lymphoma (n = 19, 90.5%) showed unilateral involvement, demonstrating a statistically significant predominance over inflammatory etiologies (P = 0.02). Although extraconal fat involvement was observed in both cohorts, it was more frequent in inflammatory cases (P = 0.036).

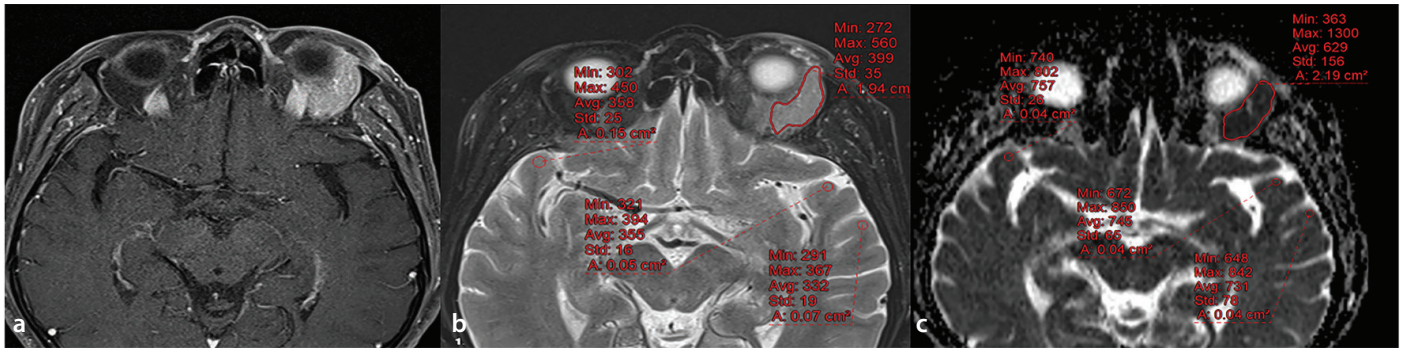

Figure 2. Representative example of lesion and reference cortical measurements in a patient with orbital lymphoma; using an axial fat-saturated post-contrast T1-weighted image **(a)** as a reference, manual regions of interest (ROIs) were placed to avoid cystic/necrotic components and lesion margins on the axial fat-saturated T2-weighted image **(b)** and apparent diffusion coefficient map **(c)**; reference cortical ROIs were positioned in normal-appearing cortex while carefully avoiding white matter and sulci.

MRI examinations were performed using 3 T scanners for 10 patients (3 lymphoma, 7 inflammatory) and 1.5 T scanners for 48 patients (18 lymphoma, 30 inflammatory). Mean T2 signal ratios and mean ADC values and ratios for each reviewer are presented in Table 2. All measurements showed statistically significant differences between the two cohorts ($P < 0.05$). Lymphomas demonstrated significantly lower ADC values/ratios and higher T2 signal ratios than inflammatory lesions. Interobserver variability in measurements showed excellent agreement, with ICC values ranging from 0.969 to 0.985.

ROC analysis using measurements from both reviewers is presented in Figure 3. The highest diagnostic performance was achieved by the ADC ratio measurements from Reviewer 1, with an area under the curve (AUC) of 0.920 (95% CI: 0.818–0.975, $P < 0.001$). Using the optimal cut-off (≤1), it demonstrated 85.7% sensitivity and 86.5% specificity, with an overall accuracy of 86.2%. The positive and negative predictive values were 78.3% and 91.4%, respectively.

The T2 signal ratio demonstrated moderate diagnostic performance, with an AUC of 0.726 (95% CI: 0.592–0.86, $P = 0.001$) for Reviewer 1. At the optimal cut-off (>0.88), the test achieved 80.95% sensitivity and 64.86% specificity, yielding an overall accuracy of 70.7%, with positive and negative predictive values of 56.7% and 85.7%, respectively.

The OR rule combination (applying either ADC ratio ≤1 or T2 signal ratio >0.88) showed a sensitivity of 95.2% and specificity of 56.8%. The AND rule combination (requiring both ADC ratio ≤1 and T2 signal ratio >0.88) resulted in a sensitivity of 71.4% and specificity of 94.6%.

Table 1. Comparison of descriptive characteristics

	Lymphoma (%)	Inflammation (%)	*P* value
Laterality			
Unilateral	19 (90.5%)	23 (62.2%)	0.02
Bilateral	2 (9.5%)	14 (37.8%)	
Location			
Extraconal space only	12 (57.1%)	24 (64.9%)	0.036
Intraconal space only	3 (14.3%)	0	
Both extra- and intraconal space	5 (23.8%)	13 (35.1%)	
Muscle cone only	1 (4.8%)	0	

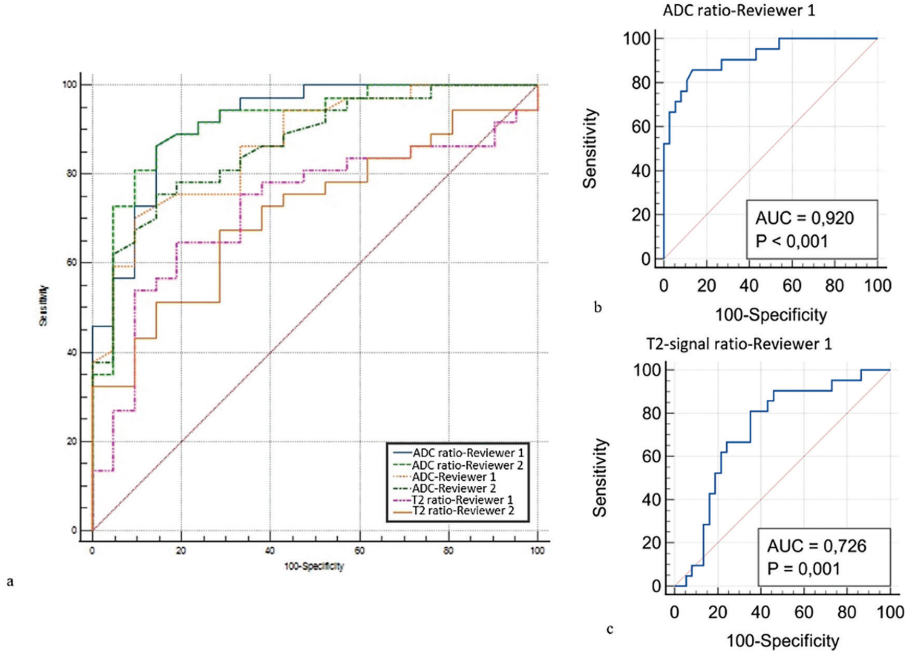

Figure 3. Receiver operating characteristic curve analysis evaluating the diagnostic performance of apparent diffusion coefficient (ADC) and transverse relaxation time (T2) signal ratio measurements between reviewers **(a)**; ADC ratio measurements by Reviewer 1 demonstrated superior diagnostic performance, with an area under the curve (AUC) of 0.920 ($P < 0.001$) **(b)**; among T2 signal ratio measurements, Reviewer 1's results showed moderate diagnostic value, with an AUC of 0.726 ($P = 0.001$) **(c)**.

Discussion

This study demonstrates that combining the T2 signal ratio with ADC values considerably improves differentiation between orbital lymphoma and its challenging inflammatory mimics, particularly IgG4-ROD and granulomatous inflammation (Figure 4). The ADC ratio demonstrated superior diagnostic performance (AUC: 0.920; sensitivity: 85.7%; specificity: 86.5%), confirming the role of DWI as the primary discriminator for lymphoma detection. Although the T2 signal ratio alone exhibited only moderate discriminatory capability (AUC: 0.726; sensitivity: 80.95%; specificity: 64.86%), its integration with ADC values enhanced diagnostic power through complementary effects: the OR rule achieved 95.2% sensitivity, whereas the AND rule demonstrated 94.6% specificity.

Consistent with the known epidemiology of orbital lymphomas, which typically present in the 6th to 7th decades, our patients with lymphoma were significantly older than those with inflammatory disease ($P = 0.002$), as previously documented.[4,5] Our findings also align with earlier studies demonstrating the predominance of unilateral involvement in orbital lymphoma.[4,17] Although extraconal space involvement was frequent in the lymphoma group, supporting the findings of Priego et al.[17], we observed it to be more prevalent in inflammatory cases ($P = 0.036$).

Both reviewers demonstrated significantly lower mean ADC values and ratios in lymphoma ($P < 0.001$). These findings align with prior studies employing various DWI techniques, including single-shot echo-planar imaging (EPI), turbo spin-echo DWI, and diffusion-sensitized driven-equilibrium preparation.[4,6,7,18] Although non-EPI DWI techniques offer advantages over conventional EPI—such as reduced susceptibility artifacts and geometric distortion—all approaches consistently demonstrate lymphoma's characteristic ADC reduction compared with IgG4-ROD and other inflammatory conditions. These findings support the diagnostic utility of DWI independent of technique, although standardization of protocols could further improve its clinical application. Despite DWI's established role in differentiating orbital lymphoma from inflammatory mimickers, diagnostic challenges persist in certain cases. This challenge is especially evident in IgG4-ROD and granulomatous orbital diseases, where ADC values are frequently reduced compared with IOI. Notably, lacrimal gland involvement in IgG4-ROD often demonstrates ADC values below 600 × 10^{-6}

Table 2. Inter-reviewer agreement and comparison of T2 signal ratios and ADC values/ratios between the lymphoma and inflammation groups

	Lymphoma	Inflammation	*P* value	ICC
Mean T2 signal ratio				
Reviewer 1	0.961 ± 0.134	0.822 ± 0.242	0.007	0.969
Reviewer 2	0.980 ± 0.146	0.835 ± 0.267	0.01	
Mean ADC lesion ($\times 10^{-3}$ mm^2/s)				
Reviewer 1	0.731 ± 0.172	1.077 ± 0.261	<0.001	0.985
Reviewer 2	0.713 ± 0.173	1.058 ± 0.262	<0.001	
Mean ADC ratio				
Reviewer 1	0.864 ± 0.184	1.319 ± 0.311	<0.001	0.971
Reviewer 2	0.852 ± 0.180	1.333 ± 0.336	<0.001	

T2, *transverse relaxation time; ADC, apparent diffusion coefficient.*

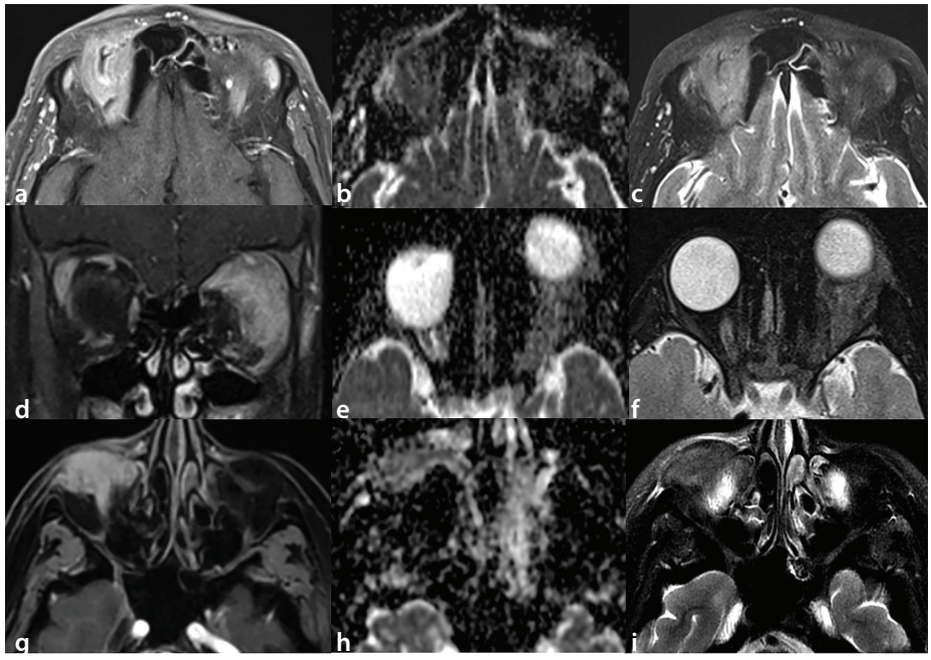

Figure 4. Space-occupying soft tissue masses with diffuse contrast enhancement on post-contrast T1-weighted images were observed in 3 patients diagnosed with primary orbital lymphoma (**a**), immunoglobulin G4-related orbital disease (IgG4-ROD) (**d**), and sarcoidosis (**g**); these lesions demonstrated overlapping apparent diffusion coefficient (ADC) values on ADC maps (**b**, **e**, and **h**, respectively); transverse relaxation time (T2)-weighted images helped differentiate lymphoma (**c**) from IgG4-ROD and sarcoidosis (**f** and **i**, respectively), with lymphoma appearing isointense to the cerebral cortex, whereas the inflammatory mimickers appeared hypointense.

mm^2/s.[10,11] Granulomatous inflammations may similarly exhibit ADC values overlapping with lymphoma.[19] For cases with indeterminate ADC measurements, additional discriminative imaging features become essential to accurately distinguish lymphoma from IgG4-ROD and granulomatous inflammation, ensuring appropriate clinical management.

Advanced MRI techniques, including dynamic contrast-enhanced (DCE) MRI and arterial spin labeling (ASL), have demonstrated diagnostic potential for differentiating orbital lymphoma from benign mimics. Hu et al.[5] reported that DCE-MRI parameters, particularly "$_{Ve}$" with 76.2% sensitivity and 94.9% specificity, could reliably distinguish malignant lymphoproliferative disorders from benign lesions based on their distinct microvascular characteristics. Eissa et al.[20] reported that total blood flow derived from ASL could discriminate lymphoma from idiopathic inflammatory pseudotumor ($P < 0.001$), although ADC provided superior diagnostic accuracy compared with ASL, and the combined use of both techniques yielded only minimal improvement over ADC alone, suggesting limited clinical added value for ASL. Although perfusion MRI parameters demonstrate promising discriminatory capability for differentiating orbital lymphoma from benign lymphoproliferative and inflammatory disorders, their clinical application has several limitations. Perfusion imaging is not currently part of standard orbital MRI protocols; its inclusion would prolong scan times, and the requirement for specialized post-processing further restricts its viability in daily practice. These limitations underscore the need for practical MRI biomarkers, notably those available through T2-weighted imaging.

Granulomatous inflammations and IgG4-related disease are well-recognized causes of T2-hypointense head and neck lesions. Characteristics of the T2 signal arise from granulomas in granulomatous diseases, including GPA and sarcoidosis, and from fibrosis in orbital IgG4-related disease.[9-12] In contrast, orbital lymphoma is mostly reported to present with an intermediate T2 signal.[13] Our results align well with the literature, as the mean T2 signal ratio of the inflammation cohort was considerably lower than that of the lymphoma cohort.

Although the T2 signal ratio yielded lower isolated diagnostic reliability than ADC values, it serves as a strong complementary tool that considerably enhances the discriminatory power of ADC. The combined application of both parameters using the OR rule (ADC ratio ≤1 or T2 signal ratio >0.88) demonstrated superior sensitivity (95.2%) compared with ADC alone (85.7%). More importantly, the AND rule combination (ADC ratio ≤1 and T2 signal ratio >0.88), achieved higher specificity (from 86.5% to 94.6%), effectively reducing false-positive cases while maintaining diagnostic reliability. These findings underscore that T2-weighted imaging contributes meaningfully to diagnostic confidence, particularly in equivocal cases where ADC values are borderline. Importantly, this approach has direct clinical utility, as it relies on standard MRI sequences without requiring specialized protocols, offering radiologists a practical method to guide patient management.

This study has several limitations, primarily inherent to its retrospective design. The multi-vendor nature of our MRI data (1.5 T and 3 T scanners from different manufactur-

ers) and variations in acquisition parameters may introduce technical variability in quantitative measurements, despite our standardization efforts using ratio-based analyses. Additionally, the small number of patients scanned at 3 T MRI (n = 10) limited our ability to evaluate field strength effects, warranting investigation in future larger studies. Another technical consideration is the use of EPI-DWI, which is particularly susceptible to artifacts and geometric distortion near bone–air interfaces, potentially compromising ADC measurements in small orbital lesions. Our inflammatory cohort demonstrated marked heterogeneity in subgroup distribution, with notably limited cases of sarcoidosis and fungal angiitis, which may affect the generalizability of our findings across all inflammatory subtypes. Furthermore, the retrospective design and modest sample size (n = 58) preclude advanced quantitative analyses such as radiomics, which typically require larger cohorts with standardized imaging protocols to ensure reproducible feature extraction.

In conclusion, the combined evaluation of ADC values and T2 signal ratio provides a clinically practical and effective method for differentiating orbital lymphoma from its challenging inflammatory mimics. This approach utilizes routine MRI sequences while demonstrating superior diagnostic performance compared with either parameter in isolation. Because accurate differentiation between these entities carries substantial therapeutic implications, our findings may help optimize patient management. Multicenter prospective studies with standardized protocols are needed to validate optimal cut-off values and guide clinical implementation.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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