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Orbital Imaging in Animal Models of Orbital and Ocular Adnexal Diseases: A Systematic Review

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 7 June 2025 and was last updated on 7 June 2025.

INTRODUCTION

Review question / Objective Review Question:
Population (P): Animal models (e.g., rodents, canines, primates) used to study orbital and ocular adnexal diseases
Intervention (I): Application of orbital imaging modalities (e.g., MRI, CT, DTI, PET, SPECT, molecular imaging)
Comparator (C): Conventional methods without imaging or alternative imaging modalities (where applicable)
Outcomes (O): Diagnostic accuracy, visualization of anatomical or functional changes, longitudinal disease monitoring, reduction in animal use, and assessment of therapeutic interventions
Study Design (S): Preclinical in vivo studies reporting original imaging data in animal models of orbital diseases

Objective:
To systematically evaluate how various orbital imaging modalities have been applied in animal models of orbital and ocular adnexal diseases, and to assess their diagnostic utility, contributions to mechanistic understanding, and role in enhancing ethical and translational preclinical research.

Rationale Orbital and ocular adnexal diseases affect critical structures such as the optic nerve, extraocular muscles, and orbital bones, leading to significant visual and functional impairments. Animal models play a crucial role in understanding the pathophysiology of these diseases and in developing new therapies. However, traditional research methods often rely on invasive procedures that limit longitudinal assessment and violate the 3R principles (Replacement, Reduction, Refinement) of animal research.

Orbital imaging modalities—such as MRI, CT, DTI, PET, and molecular imaging—offer non-invasive alternatives that enable real-time, longitudinal monitoring of disease progression and treatment response in live animals. Despite their increasing use, a systematic evaluation of how these modalities are applied across disease types, their diagnostic value, and methodological challenges is lacking. This review addresses this gap by synthesizing current evidence on imaging strategies in animal models of orbital disease, aiming to inform future research design, promote ethical practices, and enhance translational relevance.

Condition being studied Orbital and ocular adnexal diseases in animal models, including inflammatory (e.g., thyroid eye disease, optic neuritis), neoplastic (e.g., optic glioma, rhabdomyosarcoma), genetic (e.g., Crouzon syndrome, Leber hereditary optic neuropathy), neuromuscular (e.g., strabismus), and traumatic disorders (e.g., orbital fractures, traumatic optic neuropathy).

METHODS

Search strategy This systematic review was conducted in accordance with the PRISMA guidelines. A comprehensive literature search was performed across four major databases: PubMed, Web of Science, Embase, and the Cochrane Library. The search strategy used a combination of MeSH terms and free-text keywords related to orbital disease, ocular adnexal disease, animal models, and imaging techniques. Boolean operators (AND, OR) were used to refine results.

Example search string (PubMed): ("orbital disease" OR "ocular adnexal") AND ("animal model*" OR "mice" OR "mouse" OR "rat" OR "rabbit" OR "canine" OR "primate") AND ("imaging" OR "MRI" OR "magnetic resonance imaging" OR "CT" OR "computed tomography" OR "diffusion tensor imaging" OR "DTI" OR "PET" OR "SPECT" OR "molecular imaging")

The search included all articles published up to May 2024, with no language restrictions initially applied. Additional studies were identified by screening the references of included articles. Only original studies reporting orbital imaging in animal models with translational relevance were included.

Participant or population Preclinical in vivo animal models used to study orbital and ocular adnexal diseases. These include rodent models (e.g., mice, rats), rabbits, canines, and non-human primates. The selected studies involve healthy or genetically modified animals or those with experimentally induced conditions that mimic human orbital diseases, such as thyroid eye disease, optic neuritis, glioma, craniofacial syndromes, strabismus, and orbital trauma.

Intervention The interventions of interest are orbital imaging techniques applied in animal models to study orbital and ocular adnexal diseases. These include structural and functional imaging modalities such as:

Magnetic Resonance Imaging (MRI), including T1-, T2-weighted, DTI, DWI, MEMRI, and functional MRI
Computed Tomography (CT) and Micro-CT
Diffusion Basis Spectrum Imaging (DBSI)
Positron Emission Tomography (PET)
Single-Photon Emission Computed Tomography (SPECT)
Molecular imaging using targeted radiotracers (e.g., IGF-1R probes)

These imaging methods are used to diagnose, monitor, and evaluate disease progression and treatment effects non-invasively.

Comparator Where applicable, comparators include:
- Conventional histopathological or ex vivo methods used to assess orbital disease (e.g., tissue dissection, microscopy)
- Alternative imaging modalities (e.g., MRI vs. CT)
- Baseline or untreated control groups in imaging-based intervention studies
- Imaging in healthy animal models versus diseased models

In many included studies, the imaging modality is evaluated for its standalone diagnostic or monitoring utility without a direct comparator, particularly in exploratory or model-validation research.

Study designs to be included This review will include original preclinical in vivo studies that apply orbital imaging techniques in animal models of orbital and ocular adnexal diseases. Eligible study designs include: (1) Controlled or uncontrolled experimental studies (2)Longitudinal imaging studies (3) Cross-sectional imaging assessments with original quantitative or qualitative imaging data.

Eligibility criteria Inclusion criteria:
- Original in vivo animal studies involving models of orbital or ocular adnexal diseases (e.g.,

inflammatory, neoplastic, genetic, neuromuscular, or traumatic conditions)
- Studies that apply orbital imaging techniques such as MRI, CT, DTI, PET, SPECT, or molecular imaging
- Studies reporting original imaging data, either qualitative or quantitative
- Studies with translational relevance to human orbital disease
- Full-text articles published in peer-reviewed journals

Exclusion criteria:
- In vitro, ex vivo, or computational-only studies
- Clinical studies involving human participants
- Reviews, meta-analyses, editorials, commentaries, or conference abstracts without full data
- Studies that do not involve imaging, or where imaging is unrelated to orbital or ocular adnexal disease
- Articles not available in full text.

Information sources The following electronic databases were searched: PubMed, Web of Science, Embase, and the Cochrane Library. Additional relevant studies were identified through manual screening of reference lists from included articles. All searches covered literature published up to May 2024. No language restrictions were applied during the initial search phase.

Main outcome(s)
- Diagnostic utility of orbital imaging modalities in detecting structural or functional changes in animal models of orbital and ocular adnexal diseases
- Imaging-based characterization of disease features (e.g., edema, inflammation, tumor growth, bone remodeling, nerve integrity)
- Longitudinal monitoring of disease progression or treatment response using non-invasive imaging
- Contribution to ethical research through reduction in animal use and support of 3R principles (Replacement, Reduction, Refinement).

Quality assessment / Risk of bias analysis Risk of bias in the included animal studies will be assessed using the SYRCLE's Risk of Bias tool, which is specifically designed for preclinical in vivo studies. This tool evaluates potential biases across domains such as selection, performance, detection, attrition, reporting, and other sources. Two independent reviewers will conduct the assessment, and any disagreements will be resolved through discussion or consultation with a third reviewer to ensure consistency and objectivity.

Strategy of data synthesis A qualitative synthesis will be conducted due to the heterogeneity of imaging modalities, animal models, disease categories, and outcome measures. Included studies will be grouped by disease type (e.g., inflammatory, neoplastic, genetic, neuromuscular, traumatic) and by imaging modality (e.g., MRI, CT, DTI, PET/SPECT, molecular imaging).

For each group, key findings will be extracted and compared in terms of diagnostic value, structural/functional insights, longitudinal monitoring capability, and translational relevance. Descriptive tables and figures will be used to summarize imaging applications, model characteristics, and study outcomes.

A meta-analysis will not be performed due to the expected variability in study designs and outcome metrics.

Subgroup analysis
If data allows, subgroup analyses will be performed based on:
- Disease category (e.g., inflammatory vs. neoplastic vs. genetic disorders)
- Imaging modality (e.g., structural MRI vs. functional MRI vs. CT vs. molecular imaging)
- Animal species/model (e.g., rodent vs. rabbit vs. primate)
- Study objective (e.g., diagnosis, disease monitoring, treatment evaluation)
- Imaging outcome type (e.g., anatomical vs. functional vs. molecular)
These subgroup analyses aim to explore patterns in imaging application, diagnostic performance, and translational utility across different research contexts.

Sensitivity analysis Sensitivity analysis will be conducted to assess the robustness of the findings by:
- Excluding studies rated as high risk of bias based on the SYRCLE tool
- Excluding studies with unclear or incomplete imaging outcome reporting
- Comparing results with and without non-rodent models to evaluate species-specific variability
- Assessing the impact of older vs. more recent studies to account for advancements in imaging technology.

Country(ies) involved China, Malaysia.

Keywords Orbital imaging; Animal models; Ocular adnexal diseases.

Contributions of each author

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