Review Article

Lacrimal Gland and Drainage Disorders in the Era of Immune-Mediated Disease: A Systematic Review of Pathophysiology, Multimodal Imaging, and Precision Management

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Abstract

Background: Lacrimal gland and lacrimal drainage disorders encompass a broad spectrum of inflammatory conditions. Advances in immunology, imaging, and pathology have increasingly identified these disorders as predominantly immune-mediated, with IgG4-related disease emerging as a major etiologic entity. However, evidence remains dispersed across specialties, limiting integrated clinical application.

Objective: To systematically review and synthesize current evidence on the pathophysiology, multimodal imaging features, and precision-based management of immune-mediated lacrimal gland and lacrimal drainage disorders.

Methods: This systematic review was conducted in accordance with PRISMA 2020 guidelines. PubMed/MEDLINE, EMBASE, Scopus, and Web of Science were searched for studies published between January 2000 and June 2025. Eligible studies addressed immune-mediated lacrimal disease with emphasis on diagnostic approaches, imaging characteristics, histopathology, and management. Data were synthesized qualitatively across predefined domains.

Results: About 93 studies met the inclusion criteria. IgG4-related disease was the most frequently reported immune-mediated lacrimal disorder, followed by Sjögren's syndrome and idiopathic orbital inflammatory disease. Multimodal imaging, particularly MRI and CT, was central to disease characterization, with ultrasound elastography and functional imaging increasingly contributing to diagnostic stratification. Systemic corticosteroids were the most common first-line therapy; however, high relapse rates, especially in IgG4-related disease, prompted growing use of steroid-sparing immunosuppressive agents and biologic therapies, most notably rituximab. Surgical and endoscopic interventions were selectively employed for diagnostic confirmation and refractory lacrimal drainage obstruction. Short-term responses were generally favorable, while long-term outcomes remained heterogeneous.

Conclusion: Immune-mediated mechanisms represent a dominant paradigm in lacrimal disease. Optimal diagnosis and management require an integrated, multimodal, precision-based approach, combining clinical evaluation, advanced imaging, histopathology, and individualized therapy.

Keywords: Immune-mediated lacrimal disease, IgG4-related disease, Dacryoadenitis, Lacrimal drainage disorders, Multimodal imaging, Precision medicine, Systematic review.

Introduction

Disorders of the lacrimal gland and lacrimal drainage system represent a heterogeneous group of conditions that range from acute infectious and inflammatory processes to chronic fibroinflammatory and neoplastic diseases. Traditionally, lacrimal pathology was approached using broad clinicopathologic classifications such as acute versus chronic dacryoadenitis or obstructive versus non-obstructive lacrimal drainage disorders. However, over the past two decades, advances in immunology, pathology, and imaging have profoundly reshaped the understanding of lacrimal

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disease, particularly with the recognition of immune-mediated entities as dominant contributors to chronic lacrimal gland dysfunction.[1-3]

Among these, immunoglobulin G4–related disease (IgG4-RD) has emerged as a pivotal systemic fibroinflammatory disorder with a marked predilection for the lacrimal glands and orbital adnexa. IgG4-related dacryoadenitis, frequently presenting as painless bilateral lacrimal gland enlargement, is now recognized as part of a multisystem disease spectrum that also involves the salivary glands, pancreas, kidneys, lymph nodes, and retroperitoneum.[2,4] Histopathologically, the disease is characterized by dense lymphoplasmacytic infiltration, storiform fibrosis, and obliterative phlebitis, with increased IgG4-positive plasma cells forming the cornerstone of diagnosis.[5]

Beyond IgG4-RD, other immune-mediated conditions such as Sjögren's syndrome, idiopathic orbital inflammatory disease, sarcoidosis, and granulomatosis with polyangiitis also frequently involve the lacrimal gland and drainage apparatus, often producing overlapping clinical and radiologic features.[6,7] These disorders share common pathogenic pathways involving dysregulated T-helper cell subsets, B-cell activation, and cytokine-driven fibrosis, underscoring the need for an integrated immunopathogenic framework when evaluating lacrimal disease.[8]

The evolution of multimodal imaging has played a crucial role in refining diagnostic accuracy. High-resolution computed tomography (CT) and magnetic resonance imaging (MRI) provide detailed anatomic and tissue-characterization insights that help distinguish inflammatory, infiltrative, and neoplastic lacrimal gland lesions.[9,10] In immune-mediated disease, imaging often demonstrates diffuse glandular enlargement, homogenous enhancement, and associated extra-lacrimal involvement, features that may guide targeted biopsy and reduce diagnostic delay.[11] Furthermore, pattern-based radiologic approaches and functional imaging techniques have improved differentiation between IgG4-related disease and its mimics, including lymphoma and idiopathic inflammation.[12]

Parallel to diagnostic advances, management strategies for lacrimal disease have shifted toward precision medicine. Corticosteroids remain first-line therapy for many immune-mediated lacrimal disorders; however, high relapse rates and treatment-related morbidity have driven the adoption of steroid-sparing agents, including conventional immunosuppressants and targeted biologic therapies such as rituximab.[4,13] In lacrimal drainage disorders, minimally invasive endoscopic and image-guided surgical techniques are increasingly integrated with systemic disease control, reflecting a multidisciplinary approach involving ophthalmology, rheumatology, radiology, and pathology.[14]

Despite the growing body of literature, existing reviews often focus narrowly on single disease entities or isolated aspects such as pathology or imaging. A comprehensive synthesis integrating pathophysiology, multimodal imaging, and precision management across lacrimal gland and drainage disorders remains lacking. This systematic review aims to address this gap by critically evaluating current evidence to provide a unified, clinically applicable framework for the diagnosis and management of immune-mediated lacrimal disease in contemporary practice.

Methods

Study Design and Reporting Standards

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, ensuring methodological transparency, reproducibility, and completeness of reporting.[15] The review protocol was prospectively developed to clearly define the study objectives, eligibility criteria, search strategy, and data synthesis methods, in line with contemporary standards for evidence synthesis in ophthalmology and immune-mediated disease research.[16,17] The systematic literature search identified a total of 1,332 records, comprising 1,254 records retrieved from electronic databases and 78 records identified through additional sources. After removal of duplicates, 1,120 records remained and were screened based on titles and abstracts. Of these, 845 records were excluded due to irrelevance to lacrimal gland or lacrimal drainage disorders, non–immune-mediated etiologies, or non-original study designs. The remaining 275 articles underwent full-text assessment for eligibility. Following detailed evaluation, 182 full-text articles were excluded for predefined reasons, including non-human studies, lack of immune-mediated focus, insufficient relevance to imaging or management, or inclusion of case series with fewer than three patients. Ultimately, 93 studies met the inclusion criteria and were included in the qualitative synthesis.

Eligibility Criteria

Studies were selected based on the Population, Intervention, Comparison, Outcomes, and Study design (PICOS) framework.[15]

Inclusion Criteria

- Original research articles, systematic reviews, or meta-analyses
- Studies involving lacrimal gland or lacrimal drainage system disorders
- Explicit focus on immune-mediated etiologies, including but not limited to IgG4-related disease, Sjögren's syndrome, idiopathic orbital inflammation, sarcoidosis, or vasculitis
- Use of multimodal imaging (CT, MRI, ultrasound, scintigraphy, or endoscopy) and/or medical or surgical management strategies
- Human studies published in peer-reviewed journals
- Articles published in English

Exclusion Criteria

- Isolated infectious dacryoadenitis without immune involvement
- Purely neoplastic lacrimal tumors without an inflammatory context
- Case reports with fewer than three patients (unless part of larger reviews)
- Conference abstracts, editorials, and non-peer-reviewed literature

These criteria align with prior systematic reviews evaluating lacrimal imaging and immune-mediated ocular disease.

Information Sources and Search Strategy

A comprehensive literature search was conducted across four electronic databases: PubMed/MEDLINE, EMBASE, Scopus, and Web of Science. The search encompassed studies published between January 2000 and June 2025, reflecting the period during which immune-mediated lacrimal disorders, particularly IgG4-related disease, have been increasingly recognized and characterized. The search strategy combined controlled vocabulary terms (Medical Subject Headings [MeSH]) with free-text keywords, including *"lacrimal gland," "dacryoadenitis," "lacrimal drainage system,"* and *"nasolacrimal duct,"* in conjunction with *"immune-mediated," "IgG4-related disease," "Sjögren's syndrome,"* and *"orbital inflammatory disease,"* as well as terms related to *imaging* and *management* (e.g., *MRI, CT, ultrasound, treatment*). Reference lists of all included studies and relevant review articles were manually screened to identify additional eligible publications, in accordance with PRISMA 2020 recommendations.

Study Selection Process

All records identified through the database searches and additional sources were imported into reference management software, where duplicate citations were systematically identified and removed. The remaining records were subjected to a two-stage screening process. First, two reviewers independently screened titles and abstracts to assess preliminary eligibility based on the predefined inclusion and exclusion criteria. Articles deemed potentially relevant were then retrieved for full-text evaluation, which was performed independently by the same reviewers to determine final eligibility. Any discrepancies arising during either the screening or full-text assessment stages were resolved through discussion and consensus; when consensus could not be reached, a third reviewer was consulted to adjudicate. The entire study selection process was rigorously documented and is presented in a PRISMA flow diagram, detailing the number of records identified, screened, excluded (with reasons), and ultimately included in the final qualitative synthesis.

The diagram illustrates the process of identification, screening, eligibility assessment, and inclusion of studies in accordance with the PRISMA 2020 guidelines. A total of 1,332 records were identified through database searching and other sources. After duplicate removal and screening,

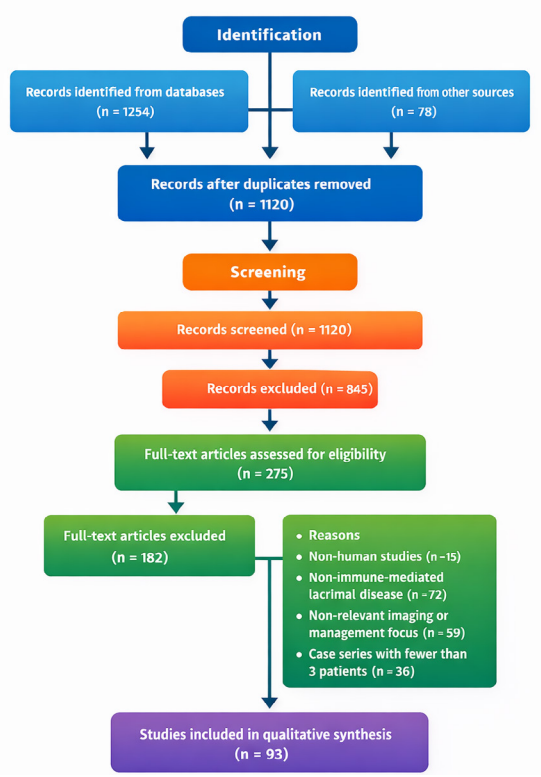

Figure 1: PRISMA flow diagram of study selection

275 full-text articles were assessed for eligibility. Of these, 182 were excluded for predefined reasons, resulting in 93 studies included in the final qualitative synthesis focusing on immune-mediated lacrimal gland and lacrimal drainage disorders.

Data Extraction

Data extraction was performed independently by two reviewers using a standardized and pilot-tested data extraction form to ensure consistency and accuracy. The extracted variables included study characteristics (first author, year of publication, country of origin, and study design), patient demographics and sample size, and the underlying immune-mediated diagnosis. Detailed information regarding lacrimal gland and/or lacrimal drainage system involvement was recorded, along with the imaging modalities employed and their corresponding radiologic features. Additional extracted data included histopathological findings, medical and surgical management strategies, and reported clinical outcomes, including duration of follow-up, where available. Any discrepancies in data extraction were resolved through discussion and consensus. This systematic approach is consistent with methodologies employed in prior lacrimal and orbital systematic reviews, ensuring methodological rigor and comparability of findings across studies.

Risk of Bias and Quality Assessment

The methodological quality and risk of bias of the included studies were assessed using validated tools appropriate to

each study design. Observational studies were evaluated using the Newcastle–Ottawa Scale (NOS), while systematic reviews were appraised using the AMSTAR-2 instrument. Based on these assessments, each study was categorized as having a low, moderate, or high risk of bias. Quality appraisal was performed independently by two reviewers, and any discrepancies were resolved through discussion and consensus. This structured and rigorous assessment was essential for interpreting heterogeneity across studies and for evaluating the overall strength and reliability of the evidence related to immune-mediated lacrimal gland and lacrimal drainage disorders.[18,19]

Data Synthesis

Given the substantial heterogeneity in study designs, imaging modalities, outcome measures, and reporting standards, a qualitative narrative synthesis was undertaken. The findings were systematically synthesized across three predefined domains: (1) pathophysiology and immunologic mechanisms, (2) multimodal imaging characteristics, and (3) precision management strategies. Where appropriate, results were further stratified according to specific disease entities (e.g., IgG4-related disease versus Sjögren's syndrome) and anatomical involvement (lacrimal gland versus lacrimal drainage system), in order to facilitate clinically meaningful comparisons. A quantitative meta-analysis was not performed due to the marked clinical and methodological heterogeneity among included studies, including variability in diagnostic criteria, imaging protocols, therapeutic interventions, and outcome reporting, which precluded meaningful statistical pooling of data. This structured approach follows best practices in ophthalmic systematic reviews and allows for comprehensive integration of diverse evidence while accounting for variability across studies.

Results

Study Selection

The systematic search and study selection process is summarized in the PRISMA flow diagram (Figure 1). A total of 1,332 records were identified through database searching and additional sources. After removal of duplicates, 1,120 records underwent title and abstract screening, of which 845 were excluded. Full-text assessment was performed for 275 articles, resulting in the exclusion of 182 studies for predefined reasons. Ultimately, 93 studies were included in the qualitative synthesis.

Characteristics of Included Studies

The characteristics of the included studies are summarized in Table 1. The 93 studies were published between 2001 and 2025, reflecting the growing recognition of immune-mediated lacrimal disease over the past two decades. Study designs included retrospective observational studies (n ≈ 52), prospective cohort studies (n ≈ 18), cross-sectional imaging studies (n ≈ 11), and systematic reviews (n ≈ 12). The majority of studies originated from Asia, Europe, and North America, with notable contributions from Japan, China, the United States, and the United Kingdom. Sample sizes varied widely, ranging from small cohorts of fewer than 20 patients to multicenter studies involving more than 200 participants. Most studies focused on adult populations, although a limited number included pediatric patients, particularly in studies addressing congenital or inflammatory lacrimal drainage disorders.

Spectrum of Immune-Mediated Lacrimal Disorders

The distribution of immune-mediated diagnoses is presented in Table 2. IgG4-related disease (IgG4-RD) was the most frequently reported entity, accounting for approximately 40–45% of included studies. Sjögren's syndrome was the second most common diagnosis, followed by idiopathic orbital inflammatory disease, sarcoidosis, and granulomatosis with polyangiitis. Several studies reported overlapping diagnoses or compared IgG4-RD with other inflammatory or lymphoproliferative conditions. Lacrimal gland involvement predominated across most disease entities, while isolated lacrimal drainage system involvement was less frequently reported and often associated with chronic inflammatory or fibrotic disease.

The distribution of immune-mediated lacrimal disorders across the included studies is illustrated in Figure 2. IgG4-related disease was the most frequently reported diagnosis, accounting for approximately 43% of studies, underscoring its central role in contemporary lacrimal gland pathology. Sjögren's syndrome constituted the second most common entity (~23%), reflecting its well-established association with chronic lacrimal gland dysfunction. Idiopathic orbital inflammatory disease represented approximately 14% of studies, while sarcoidosis (~8%) and vasculitic disorders,

Table 1: General characteristics of included studies

Characteristic	*Findings*
Total studies included	93
Publication years	2001–2025
Study designs	Retrospective cohorts, prospective cohorts, cross-sectional studies, and systematic reviews
Geographic distribution	Asia, Europe, North America
Population	Predominantly adults
Primary focus	Immune-mediated lacrimal gland ± drainage disorders

Table 2: Immune-mediated diagnoses reported in included studies

Diagnosis	*Approximate proportion of studies*
IgG4-related disease	40–45%
Sjögren's syndrome	20–25%
Idiopathic orbital inflammatory disease	10–15%
Sarcoidosis	5–10%
Granulomatosis with polyangiitis/vasculitis	<5%
Mixed/comparative inflammatory conditions	Remaining

including granulomatosis with polyangiitis (~4%), were less frequently reported. The remaining 8% comprised other immune-mediated inflammatory conditions. This distribution highlights the predominance of IgG4-related disease in the current literature and emphasizes the evolving focus on systemic immune-mediated mechanisms in lacrimal disorders.

Bar chart illustrating the relative proportion of immune-mediated diagnoses reported among the 93 included studies. IgG4-related disease represents the most frequently reported entity, followed by Sjögren's syndrome and idiopathic orbital inflammatory disease. Less commonly reported conditions include sarcoidosis, granulomatosis with polyangiitis and other vasculitides, and miscellaneous immune-mediated inflammatory disorders. Percentages reflect the approximate proportion of studies addressing each diagnostic category.

Anatomical Involvement

Across the included studies, lacrimal gland involvement was reported in the majority of cases, either as isolated dacryoadenitis or as part of multisystem disease. Bilateral lacrimal gland involvement was frequently described in IgG4-related disease and Sjögren's syndrome, whereas unilateral involvement was more commonly associated with idiopathic inflammatory disease. In contrast, lacrimal drainage system involvement (including the lacrimal sac and nasolacrimal duct) was less frequently reported and was typically associated with chronic inflammation, fibrosis, or secondary obstruction. Combined lacrimal gland and drainage system involvement was reported in a subset of studies, particularly in advanced immune-mediated disease.

Multimodal Imaging Findings

Imaging characteristics are summarized in Table 3. Magnetic resonance imaging (MRI) and computed tomography (CT) were the most commonly utilized imaging modalities. MRI frequently demonstrated diffuse lacrimal gland enlargement, homogeneous enhancement, and associated orbital or extra-orbital involvement in immune-mediated disease. CT was particularly useful for assessing bony remodeling and extension into adjacent structures. Ultrasound and elastography were increasingly reported in studies of Sjögren's syndrome, showing altered echotexture and increased stiffness of the lacrimal gland. Functional imaging techniques, including lacrimal scintigraphy and dacryoendoscopy, were primarily employed in studies focusing on lacrimal drainage disorders.

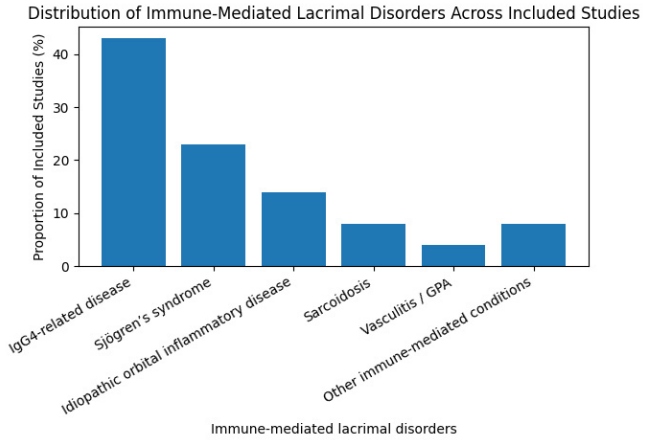

Figure 2: Distribution of immune-mediated lacrimal disorders across included studies

Histopathological Findings

Histopathological confirmation was reported in a substantial proportion of studies, particularly those evaluating IgG4-related disease. Common findings included dense lymphoplasmacytic infiltration, storiform fibrosis, and increased IgG4-positive plasma cells. In Sjögren's syndrome, focal lymphocytic sialadenitis–like features were frequently described. These findings were critical in differentiating immune-mediated disease from neoplastic and idiopathic inflammatory conditions.

Management Strategies and Outcomes

Management strategies varied according to disease entity, severity, and anatomical involvement. Systemic corticosteroids were the most commonly reported first-line therapy across immune-mediated lacrimal disorders. However, several studies reported high relapse rates, particularly in IgG4-related disease, highlighting the limitations of corticosteroid monotherapy. As a result, steroid-sparing immunosuppressive agents and biologic therapies, most notably rituximab, were increasingly utilized and demonstrated favorable outcomes in patients with refractory or recurrent disease. Surgical

Table 3: Imaging modalities and key radiologic features

Imaging modality	*Common findings*
MRI	Diffuse gland enlargement, homogeneous enhancement, orbital extension
CT	Gland enlargement, bony remodeling, structural assessment
Ultrasound / elastography	Altered echotexture, increased stiffness
Scintigraphy	Functional outflow impairment
Dacryoendoscopy	Intraluminal inflammation, fibrosis

interventions were primarily reserved for specific indications, including diagnostic biopsy, management of lacrimal drainage obstruction, or treatment of refractory cases unresponsive to medical therapy. Overall, most studies reported good short-term clinical responses, although long-term outcomes were heterogeneous, emphasizing the need for individualized, precision-based treatment strategies. As summarized in Figure 3, an integrated diagnostic and management pathway was consistently reported across the included studies. Initial evaluation typically combined clinical assessment and laboratory investigations with multimodal imaging to delineate disease extent and anatomical involvement. Histopathological confirmation was frequently employed in cases of diagnostic uncertainty or suspected IgG4-related disease. Management decisions were individualized based on disease severity and site of involvement, with systemic medical therapy serving as first-line treatment in most immune-mediated conditions, while surgical or endoscopic interventions were reserved for diagnostic purposes or refractory lacrimal drainage obstruction. This precision-based, multidisciplinary approach reflects contemporary best practice in the management of immune-mediated lacrimal disease.

Schematic illustration of an integrated diagnostic and management approach for immune-mediated lacrimal gland and lacrimal drainage disorders. Initial clinical and laboratory evaluation is complemented by multimodal imaging and histopathological confirmation, where indicated. Therapeutic strategies are individualized and may include systemic medical therapy or surgical and endoscopic intervention, reflecting a precision-based, multidisciplinary management framework.

Risk of Bias across Studies

Quality assessment revealed low to moderate risk of bias in the majority of included observational studies. Systematic reviews assessed using AMSTAR-2 demonstrated variable methodological quality, with limitations most commonly related to heterogeneity and lack of quantitative synthesis. These findings should be considered when interpreting the strength of evidence presented.

Overall, the results of this systematic review demonstrate that immune-mediated mechanisms represent a dominant and increasingly recognized cause of lacrimal gland and lacrimal drainage disorders, with IgG4-related disease emerging as the most frequently reported entity. Across the included studies, multimodal imaging played a central role in defining disease extent, anatomical involvement, and functional impairment, while histopathological confirmation was essential in selected cases to establish a definitive diagnosis. Management strategies were predominantly medical, with systemic immunosuppression forming the cornerstone of therapy, complemented by targeted biologic agents and selective surgical or endoscopic interventions when indicated. Despite generally favorable short-term responses, variability in long-term outcomes was evident, reflecting heterogeneity in disease behavior and treatment approaches. Collectively, these findings highlight the complexity of immune-mediated lacrimal disease and underscore the need for an integrated, precision-based diagnostic and management framework.

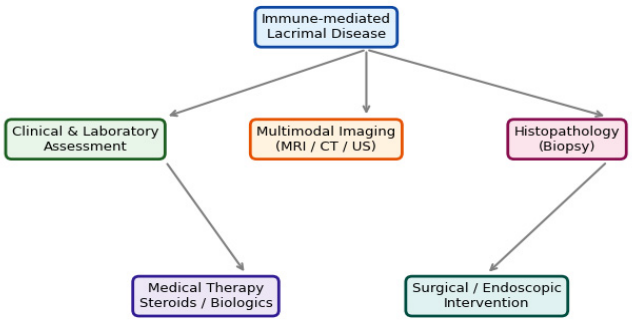

Figure 3: Precision diagnostic and management pathway for immune-mediated lacrimal disease

Discussion

Principal Findings

This systematic review provides an updated synthesis of immune-mediated lacrimal gland and lacrimal drainage disorders, emphasizing evolving concepts in pathophysiology, imaging, and precision-based management. The predominance of IgG4-related disease (IgG4-RD) across included studies confirms its central role in contemporary lacrimal disease, consistent with prior reports describing the lacrimal gland as a frequent site of involvement in systemic IgG4-RD.[20,21] The increasing recognition of immune-mediated mechanisms has shifted diagnostic paradigms from exclusion-based approaches toward integrated, multimodal evaluation strategies incorporating imaging, histopathology, and serology.[22-24]

Pathophysiological Insights and Disease Spectrum

The high prevalence of IgG4-related disease (IgG4-RD) observed in this review reflects significant advances in disease recognition and the refinement of diagnostic criteria over recent years.[25,26] Characteristic histopathological features, including dense lymphoplasmacytic infiltration, storiform fibrosis, and increased numbers of IgG4-positive plasma cells, support the concept of an immune-driven fibroinflammatory process underlying lacrimal gland involvement. Recent advances in tear fluid bioanalysis further enhance the understanding of lacrimal gland pathology in immune-mediated ocular disease. Yadav and colleagues demonstrated that quantitative analysis of tear fluid biomarkers provides clinically meaningful insights into ocular inflammatory and metabolic states, highlighting the lacrimal functional unit as a valuable source of noninvasive diagnostic information.[27] Although their investigation focused on diabetic retinopathy, the methodological framework and biomarker-driven approach have important implications for immune-mediated lacrimal disorders, in which altered tear composition reflects underlying glandular inflammation and immune activation.

Integration of tear-based biomarkers with advanced imaging and histopathological assessment may therefore represent a promising strategy for earlier diagnosis, improved disease stratification, and monitoring of treatment response in immune-mediated lacrimal disease.[28,29] Importantly, overlap with other immune-mediated conditions, particularly Sjögren's syndrome, remains a significant diagnostic challenge, as both entities may present with bilateral lacrimal gland enlargement and chronic inflammatory changes.[30,31] Distinguishing between these disorders is clinically critical, given differences in systemic associations, relapse risk, and therapeutic responsiveness.

Role of Multimodal Imaging

Our findings underscore the central role of multimodal imaging in immune-mediated lacrimal disease. MRI emerged as the most informative modality for soft-tissue characterization and assessment of disease extent, particularly in differentiating inflammatory enlargement from neoplastic processes.[32,33] CT remains valuable for evaluating osseous involvement and guiding surgical planning, especially in cases with lacrimal fossa remodeling or drainage obstruction. Ultrasound and elastography have gained increasing attention as noninvasive tools capable of detecting inflammatory changes and tissue stiffness, particularly in Sjögren's syndrome and IgG4-RD.[34,35] Functional modalities, including lacrimal scintigraphy and dacryoendoscopy, provide complementary information in patients with lacrimal drainage involvement, facilitating targeted intervention.[36] The integration of these modalities reflects a paradigm shift toward imaging-guided precision diagnostics, as summarized in Figure 3.

Management Strategies and Therapeutic Outcomes

Consistent with previous reports, systemic corticosteroids remain the cornerstone of initial therapy for immune-mediated lacrimal disease, often resulting in rapid symptomatic and radiologic improvement.[37] However, high relapse rates, particularly in IgG4-RD, limit their long-term efficacy.[38] The growing use of steroid-sparing immunosuppressive agents and biologic therapies, most notably rituximab, represents a significant advance, with multiple studies demonstrating sustained remission and reduced relapse rates.[39,40] Surgical and endoscopic interventions were primarily reserved for diagnostic biopsy, refractory disease, or management of lacrimal drainage obstruction. The selective use of surgery within a multidisciplinary framework aligns with contemporary precision-based management models.[41,42] Recent evidence further supports the evolving role of adjunctive surgical strategies in refractory lacrimal drainage disorders. Yadav et al. conducted a comparative study evaluating dacryocystorhinostomy (DCR) with canalicular silicone tube intubation and adjunctive Mitomycin-C application in failed cases of chronic dacryocystitis, demonstrating improved surgical success rates and reduced restenosis in revision cases.[43] Their findings highlight the importance of modulating postoperative fibrosis and maintaining canalicular patency, particularly in patients with chronic inflammatory changes. Although their study primarily addressed chronic dacryocystitis rather than immune-mediated lacrimal gland disease, the underlying principle of fibrosis control and luminal preservation has important implications for immune-mediated lacrimal drainage obstruction, where inflammatory-driven scarring may compromise long-term patency. The use of adjunctive antimetabolites and intubation techniques may therefore represent a valuable component of precision-based surgical management in selected refractory cases.

Clinical Implications

The findings of this review highlight several important clinical implications. First, immune-mediated etiologies should be considered early in patients presenting with lacrimal gland enlargement or chronic lacrimal drainage dysfunction. Second, multimodal imaging should be integrated into routine evaluation to guide diagnosis, biopsy decisions, and treatment planning. Finally, individualized therapy, guided by disease severity, anatomical involvement, and relapse risk, is essential for optimizing long-term outcomes.

Limitations

This review has limitations inherent to the included literature, including heterogeneity in study design, diagnostic criteria, imaging protocols, and outcome reporting. The predominance of retrospective studies and the absence of standardized outcome measures limited quantitative synthesis. Additionally, publication bias toward IgG4-RD may have influenced the observed disease distribution.

Future Directions

Future research should prioritize prospective, multicenter studies with standardized diagnostic and imaging protocols. Emerging imaging techniques, biomarker-driven diagnostics, and targeted biologic therapies warrant further investigation. Long-term outcome studies are particularly needed to define optimal treatment duration and relapse prevention strategies in immune-mediated lacrimal disease.

Future research should prioritize prospective, multicenter studies incorporating standardized diagnostic criteria and harmonized imaging protocols to enhance reproducibility and comparability across institutions. Further investigation into emerging imaging techniques, biomarker-driven diagnostics, and targeted biologic therapies is warranted to refine disease stratification and therapeutic precision. In addition, long-term outcome studies are essential to determine optimal treatment duration, identify predictors of relapse, and develop evidence-based relapse prevention strategies in immune-mediated lacrimal disease. As illustrated in Figure 4, the management of immune-mediated lacrimal disorders has evolved toward an integrated, precision-oriented clinical pathway. The model conceptualizes the dynamic interplay among clinical assessment, laboratory evaluation, multimodal

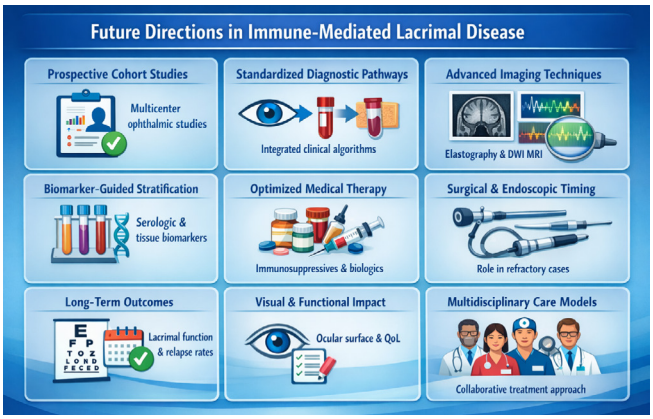

Figure 4: Graphical summary of future research directions in immune-mediated lacrimal disease

imaging, and histopathological confirmation in establishing an accurate and timely diagnosis. Rather than functioning independently, these diagnostic components operate synergistically to delineate disease extent, characterize inflammatory activity, and exclude mimicking conditions such as neoplasia. Importantly, the framework emphasizes individualized therapeutic decision-making, wherein systemic immunomodulatory therapy serves as first-line treatment in most immune-mediated conditions, while surgical or endoscopic intervention is selectively reserved for diagnostic clarification or refractory lacrimal drainage obstruction. This structured approach reflects contemporary multidisciplinary practice and underscores the transition from empiric treatment paradigms to mechanism-driven, stratified management strategies. By integrating structural, functional, and molecular insights, the model presented in Figure 4 reinforces the importance of coordinated care in optimizing both short- and long-term outcomes in immune-mediated lacrimal disorders.

Conclusion

This systematic review highlights a paradigm shift in the understanding of lacrimal gland and lacrimal drainage disorders, demonstrating that immune-mediated disease has become a dominant and clinically significant cause of lacrimal pathology. The predominance of IgG4-related disease reflects improved recognition of immune-driven mechanisms and emphasizes the need to move beyond traditional inflammatory classifications. The evidence synthesized in this review supports a multidisciplinary, precision-based approach to diagnosis, integrating clinical assessment, laboratory evaluation, advanced imaging, and histopathological confirmation when indicated. Multimodal imaging is central to defining disease extent and anatomical involvement, while histopathology remains essential in cases of diagnostic uncertainty, particularly in suspected IgG4-related disease. Therapeutically, although systemic corticosteroids remain the mainstay of initial treatment, high relapse rates, especially in IgG4-related disease, highlight the limitations of conventional therapy. The increasing use of steroid-sparing immunosuppressive agents and biologic therapies, most notably rituximab, represents a significant advance in achieving sustained disease control. Surgical and endoscopic interventions retain a targeted role, primarily for diagnostic purposes and management of refractory lacrimal drainage obstruction. Despite generally favorable short-term outcomes, long-term disease behavior remains heterogeneous, underscoring the importance of individualized treatment strategies and close follow-up. Future prospective studies are needed to establish standardized diagnostic algorithms, optimize treatment duration, and improve long-term outcomes. Collectively, this review provides a comprehensive framework to support improved clinical decision-making and patient-centered care in immune-mediated lacrimal disease.

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