Review

Damage accrual in Sjögren's disease. Prevalence, risk factors and impact on quality of life: a systematic review

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ABSTRACT

Objective. *To systematically review the prevalence, risk and associated factors of organ damage in Sjögren's disease (SjD) and to assess its impact on quality of life and long-term outcomes.*

Methods. *A systematic search of PubMed (2005-2025) identified studies assessing damage accrual in SjD. Longitudinal and cross-sectional studies enrolling patients fulfilling the 2002 AECG and/or 2016 ACR/EULAR classification criteria were included. Damage was defined using validated indices, the Sjögren's Syndrome Damage Index (SSDI) or the Sjögren's Syndrome Disease Damage Index (SSDDI), or through conceptual definitions of irreversible disease attributable injury. The lymphoma domain was excluded. Study selection followed PRISMA guidelines, and predefined PICO frameworks guided data extraction.*

Results. *Twenty-three studies were included. Glandular damage was reported in 25–86% of patients, while systemic damage affected 9–73%. Older age, longer disease duration, higher baseline ESSDAI, hypergammaglobulinaemia, hypocomplementaemia, and absence of hydroxychloroquine therapy were the most consistent predictors of damage accrual. Pulmonary and renal involvement were associated with increased mortality and hospitalisation rates. Cumulative SSDDI scores correlated with reduced health-related quality of life (HRQoL).*

Conclusion. *Organ damage in SjD is common nd progressive, reflecting sustained immunologic activity and aging-related vulnerability. Damage burden predicts poorer outcomes and diminished HRQoL. Standardisation of damage definitions and assessment tools is essential to improve comparability across studies and to guide preventive therapeutic strategies.*

Introduction

Sjögren's disease (SjD) is a chronic autoimmune disease characterised primarily by lymphocytic infiltration and destruction of the exocrine glands, leading to hallmark symptoms such as xerostomia and keratoconjunctivitis sicca. Beyond glandular involvement, SjD can also affect multiple organ systems, resulting in variable degrees of tissue and organ damage that significantly impact patient morbidity and quality of life (1, 2).

The pathophysiology of SjD is complex and involves a multifaceted interplay between genetic predisposition, environmental triggers, and immune system dysregulation. Central to disease development is the chronic autoimmune-mediated destruction of exocrine glands, primarily driven by the infiltration of autoreactive lymphocytes, particularly $CD4^+$ T cells and B cells. These immune cells produce a variety of pro-inflammatory cytokines and autoantibodies, which contribute to glandular dysfunction and tissue damage. Additionally, aberrant activation of innate immune pathways, including the type I interferon response, has been implicated in amplifying the inflammatory milieu. The sustained inflammatory environment promotes apoptosis and fibrosis within the affected tissues, ultimately leading to irreversible organ damage (3, 4).

In clinical practice, it is essential to distinguish between disease activity, a reversible inflammatory process that may fluctuate and respond to treatment, and damage, which represents the chronic, irreversible consequence of ongoing disease (5). Distinguishing between these two entities is particularly chal-

lenging in SjD and is more complex than in rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE). Common functional tests, including the Schirmer test and unstimulated salivary flow rate (USFR), are unable to reliably discriminate between activity and damage (6), complicating its measurement in clinical and research settings.

The precise definition and quantification of damage in SjD present unresolved challenges. As a result, despite its clinical relevance, only few studies have systematically investigated damage accrual in SjD or identified predictive and protective factors. Two indices have been proposed to quantify cumulative damage: the Sjögren's Syndrome Disease Damage Index (SSDDI) and the Sjögren's Syndrome Damage Index (SSDI) (7-9).

The SSDDI evaluates six domains (oral/salivary, ocular, neurologic, pulmonary, renal, and lymphoproliferative) across 15 items, with greater weights assigned to malignancy and systemic involvement (5, 9).

The SSDI, adapted from the SLICC damage index used in SLE, spans a broader range of domains, including cardiovascular, gastrointestinal, musculoskeletal and endocrine, and distinguishes Sjögren-related damage from that attributable to comorbidities or therapy (6-8).

Longitudinal data suggest that approximately 45% of SjD patients develop organ damage (excluding oral involvement) after 10 years, compared with nearly 68% of SLE patients (10, 11).

Nonetheless, both diseases are associated with comparable reductions in quality of life and functional capacity (12). These observations underscore the importance of accurate characterisation of damage in SjD, not only to refine disease monitoring but also to identify patients at risk of long-term disability and to guide tailored therapeutic strategies.

This literature review aims to investigate the prevalence and risk factors for damage accrual in patients with SjD. In addition, we explore the impact of damage on patients' quality of life and overall outcomes.

Materials and methods

Two key research questions were formulated (Q1: What is the prevalence and what are the risk factors or associated factors for damage accrual in SjD? Q2: What is the impact of damage on outcomes and quality of life in patients with SjD?). The two Population, Intervention, Comparison, and Outcomes (PICO1, PICO2) frameworks for study inclusion were developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (13) and are presented in Supplementary Table S1.

A systematic search in PubMed to identify relevant studies on damage accrual in patients with SjD was conducted. The search strategy combined terms related to the disease itself, damage and its clinical manifestations, study design and patient outcomes, including quality of life, morbidity, and mortality. The complete search strings used are reported in Supplementary Table S2.

Longitudinal studies, either retrospective or prospective in design, as well as cross-sectional studies for prevalence data were included. Only studies published in English and between 2005 and 2025 were considered. Eligible studies were required to enrol patients fulfilling established classification criteria for SjD, specifically the 2016 ACR/EULAR criteria (14) and/or the 2002 AECG criteria (15). Damage had to be defined according to validated instruments, including the SSDDI (9) and the SSDI (8), or individual domains of the SSDDI (with the exclusion of lymphoma), or alternatively through a conceptual definition of irreversible organ damage attributable to SjD. Studies were considered if they reported data on prevalence and/or risk factors for damage accrual as defined above, as well as on quality of life or outcomes associated with the presence of damage.

The lymphoma domain was excluded, as lymphoma represents a manifestation of disease activity and is currently considered a curable condition. Therefore, it should not be classified as a form of chronic or irreversible damage related to the disease.

Results

The literature search identified 248 records for PICO 1 and 348 records for PICO 2, all retrieved from PubMed. After removal of non-English articles and retracted papers, 242 records (PICO 1) and 338 records (PICO 2) were screened. Basing on title and abstract, 220 records were excluded for PICO 1 and 288 for PICO 2 due to irrelevance to the review questions. Subsequently, 7 articles for PICO 1 and 42 articles for PICO 2, were excluded after full-text review because of wrong population, inappropriate or absent definition of damage or outcomes not related to damage or prognosis. Finally, 15 studies were included for PICO 1, comprising 4 focused on glandular damage, 8 on systemic damage, and 3 addressing both glandular and systemic damage. For PICO 2, 8 studies investigating the impact of damage on quality of life, prognosis, mortality, or hospitalisation were included. A detailed overview of the study selection process is presented in the PRISMA 2020 flow diagrams (Fig. 1, 2).

A qualitative synthesis was performed to analyse the data extracted from the included studies.

PICO 1 - Glandular damage

Seven studies investigated glandular damage in patients with SjD (Table I). The studies vary in design, including prospective, retrospective, and cross-sectional approaches, and encompass different sized patient populations, ranging from 60 to over 3,000 participants.

The most frequently reported forms of glandular damage were salivary flow impairment, ocular structural abnormalities and dental damage (mainly caries and tooth loss). The prevalence of glandular damage ranged widely across studies, depending on the definition, the method and the timing of assessment. Salivary gland dysfunction was reported in 45–72% of patients, while dental caries occurred in 49–74.6%. According to Barry *et al*. (8), oral damage assessed by the SSDI, which encompasses both structural and functional components, reached a prevalence of up to 86% at one year of follow-up. Ocular damage, assessed using the SSDI, was observed

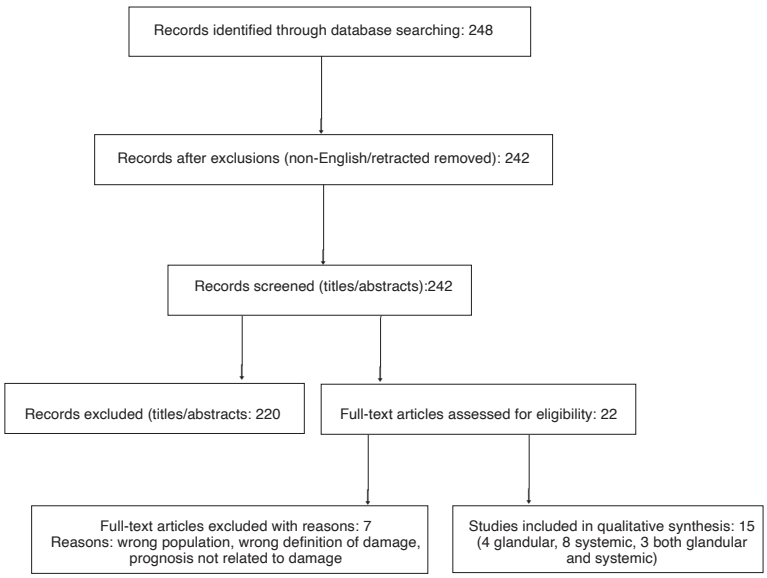

Fig. 1. PRISMA 2020 flow diagram for study selection. PICO 1: damage accrual in Sjögren's disease in grandular and systemic domains.

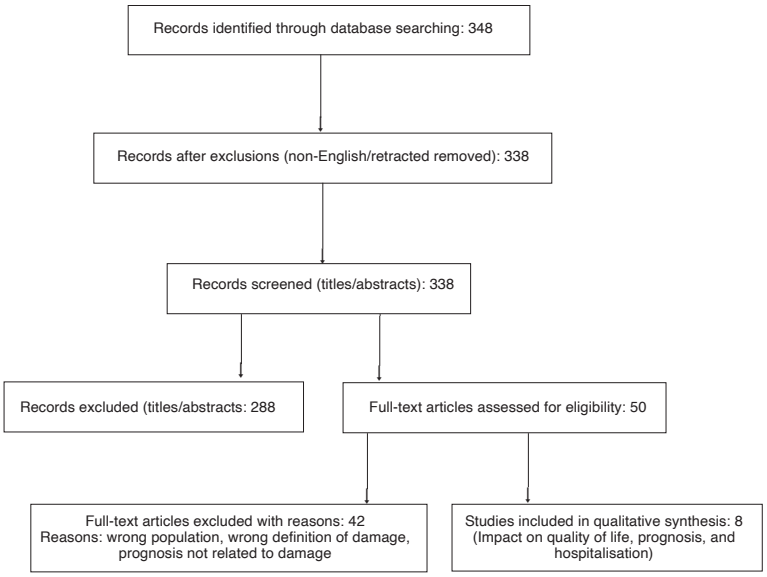

Fig. 2. PRISMA 2020 flow diagram for study selection. PICO 2: impact of damage on quality of life, prognosis and hospitalisation in Sjögren's disease.

in 25–64% of cases with a wider ocular variation with respect to oral damage. In the study by Koh *et al*. (16), structural ocular damage alone was reported with a prevalence of 76%. Persistent hypergammaglobulinaemia (IgG ≥1.6 g/L) was identified as a recurrent risk factor for salivary flow impairment in two independent cohorts (16, 17), suggesting a potential link between sustained immune activation and progressive secretory impairment. Older age and longer disease duration were also associated with an increased risk of oral and ocular damage. However, several studies note the absence of statistically significant associations, underscoring the need for further longitudinal investigations to clarify these relationships.

Overall, this summary underscores the heterogeneity in study designs and diagnostic criteria (ACR/EULAR and AECG), which may impact comparability and synthesis of findings. Nonetheless, the compiled evidence reinforces the critical role of both salivary and ocular gland involvement in SjD and supports the continued evaluation of immunological markers and clinical parameters in disease management.

PICO 1 - Systemic damage

Eleven studies investigated extra-glandular damage in SjD (Table II). The patient cohorts vary considerably in size, ranging from 51 to over 1,200 individuals, and employ diverse study designs, including prospective, retrospective, and cross-sectional methodologies. Follow-up durations vary, with some studies assessing long-term outcomes up to nearly 10 years. In most reports, systemic damage was quantified using the SSDI or SSDDI, while some studies focused on specific organ manifestations, such as renal, pleuropulmonary or neurological involvement. The reported prevalence of systemic damage ranged from 9% to 73%, reflecting considerable heterogeneity in definitions, disease duration and study design.

Cross-sectional and longitudinal studies consistently showed that higher disease activity at baseline (ESSDAI) and older age were associated with subsequent damage accrual. Persistent hypergammaglobulinaemia, low complement levels (C3, C4), and the absence of hydroxychloroquine (HCQ) use emerged as recurrent predictors of systemic damage across several cohorts (11, 16, 21, 25). In the study by Barry *et al*. (8), longer disease duration was confirmed to be a factor associated not only with greater oral and ocular damage but also with systemic involvement.

Renal involvement (including CKD, RTA, or nephrocalcinosis) was reported in 3.9–17.3% of patients and was associated with serological abnormalities (anti-SSA/SSB positivity, thrombocytopenia) and urinary abnormalities such as haematuria, proteinuria, and leukocyturia. Neurological and pulmonary damage showed a prevalence ranging from 9% to 17% across cohorts and contributed substantially to the overall SSDDI score in prospective studies (16, 26).

PICO 2

Eight studies examined the impact of damage on quality of life, prognosis, mortality and hospitalisation (Table III). These studies include large retrospective cohorts and cross-sectional analyses, with patient populations ranging from 38 to over 8,500 individuals.

Table I. Summary of studies evaluating glandular damage in Sjögren's disease (PICO 1).

Study	Patients	Study design	SjD criteria	Follow-up/ Disease duration (yrs.)	Type of damage	Prevalence (%)	Risk factors/associated factors
Barry *et al.* 2008 (8)	104	Cross-sectional and prospective	AECG	1/9	Ocular damage (SSDI) at enrolment	56	NA/Disease duration
					Ocular damage (SSDI) at 1 year	64	NA/Disease duration
					Oral damage (SSDI) at enrolment	78	NA/Disease duration
					Oral damage (SSDI) at 1 year	86	NA/Disease duration
Krylova *et al.* 2010 (10)	60	Retrospective	AECG	10	Ocular damage (SSDI)	25	NA
Koh *et al.* 2021 (16)	256	Prospective	ACR/EULAR	3/1.75	Salivary flow impairment	71	Persistent IgG levels ≥1.6 g/L
					Loss of teeth	8	NA
					Ocular structural abnormalities	76	Age at baseline
López-Morales *et al.* 2020 (17)	159	Retrospective	AECG	7/10.2	Salivary flow impairment	72	Persistent IgG levels ≥1.6 g/L
Chuang *et al.* 2020 (18)	709	Retrospective	AECG	NA/0	Dental caries	74.6	NA
Hsu *et al.* 2019 (19)	3042	Prospective	European Study Group	2.6/2.6	Dental caries	49	NA
Zabotti *et al.* 2019 (20)	75	Cross-sectional	ACR/EULAR	NA/12.4±7.2	Salivary flow impairment	45	NA

Table II. Summary of studies evaluating systemic (extra-glandular) damage in Sjögren's disease (PICO 1).

Study	Patients	Study design	SjD criteria	Follow-up/ disease duration (yrs.)	Type of damage	Prevalence (%)	Risk factors/associated factors
Barry *et al.* 2008 (8)	104	Cross-sectional and prospective	AECG	1/9	Systemic damage (SSDI) at enrolment	71	NA/Disease duration
					Systemic damage (SSDI) at 1 year	73	NA
Krylova *et al.* 2010 (10)	60	Retrospective	AECG	10	SSDI>0	45	NA
Jordán-González *et al.* 2020 (11)	100	Cross-sectional	ACR 2012	NA/5.9	SSDDI>1	39	NA/low C3 and C4, higher ESSDAI
Koh *et al.* 2021 (16)	256	Prospective	ACR/EULAR	3/1.75	Neurological/ Pleuropulmonary/renal (SSDDI defined)	9	Persistent IgG levels ≥1.6 g/L, age, anti-SSb, not using HCQ / NA
Li *et al.* 2025 (21)	351	Prospective	AECG/ACR EULAR	3/3.7	SSDDI	NA	Persistent IgG levels ≥20 g/L / NA
Duan *et al.* 2023 (22)	1288	Retrospective	AECG	2 years/ Na	CKD (eGFR<60ml/min)	12	NA/ age, urea, chlorine and anti-SSA
Cheng *et al.* 2023 (23)	79	Cross-sectional	AECG/ACR EULAR	NA/5	RTA	NA	NA/ Low peripheral Th2, Treg and NK lymphocyte count
Chatterjee *et al.* 2023 (24)	179	Retrospective	ACR/EULAR	median 1.97 years/1 year	RTA	17.3	NA
					CKD	5.6	haematuria, leukocyturia, 24h urinary protein, thrombocytopenia
Hernández-Molina *et al.* 2018 (25)	377	Retrospective	AECG	6/6	SSDI>3	45	ESSDAI, not using HCQ
Ter Borg *et al.* 2017 (26)	110	Retrospective	AECG	8.2/8.2	SNP damage	17.3	NA
					Pleuropulmonary damage	11.8	NA
Narvaez *et al.* 2020 (27)	437	Retrospective	AECG	10.4	CKD	5.2	NA
					Nephrocalcinosis	3.9	NA

Table III. Studies assessing the impact of damage on quality of life, prognosis, mortality, and hospitalisation in Sjögren's disease (PICO 2).

Study	Patients	Study design	SjD criteria	Follow-up	Type of damage	Related outcomes
Narvaez *et al.* 2020 (27)	437	Retrospective	AECG	10.4	Composite of CKD, persistent proteinuria, RTA, nephrocalcinosis, TIN or GN	More frequent hospitalisations and comorbidities in patients with renal damage
Yueting *et al.* 2024 (28)	8588	Retrospective	AECG or ACR/EULAR	4	SSDDI >2 Pulmonary fibrosis	Higher all-cause mortality (HR 1.12 (1.04–1.20)) Higher all-cause mortality (HR 1.94 (1.51–2.51))
Wang *et al.* 2020 (29)	629	Prospective	AECG or ACR/EULAR	2.6	Pulmonary hypertension	1-year mortality 6%
Atisha-Fregoso *et al.* 2015 (30)	170	Retrospective	AECG	7.7	Extra-glandular damage (SSDDI)	Higher risk of hospitalisation (OR 1.3 (1.01 - 1.66))
Brito-Zerón *et al.* 2007 (31)	266	Prospective	AECG	8.7	Parotid scintigraphy grades III or IV	Mortality
Franco *et al.* 2025 (32)	106	Cross-sectional	ACR/EULAR	NA	Articular erosions	No association with HAQ
McCoy *et al.* 2021 (33)	2961	Cross-sectional	NA	NA	Teeth loss	Association with QoL items
Stewart *et al.* 2008 (34)	38	Cross-sectional	AECG	NA	SSDDI	Correlation with the general health domain of SF-36

Follow-up durations vary considerably, extending from less than three years to over a decade, allowing for both short- and long-term outcome assessments. The features of analysed damage include systemic disease damage index (SSDDI) scores, pulmonary fibrosis, renal complications (including CKD and nephrocalcinosis), extra-glandular involvement, and dental health issues such as tooth loss.

In a large cohort of 8,588 patients (28), both a higher cumulative damage burden (SSDDI >2) and the presence of pulmonary fibrosis were associated with increased all-cause mortality (hazard ratios of approximately 1.12 and 1.94, respectively). Pulmonary hypertension was also linked to poorer short-term outcomes, with a 1-year mortality rate of 6% (29). Collectively, these findings underscore the prognostic significance of systemic and pulmonary damage domains in SjD.

Extra-glandular damage was consistently associated with greater healthcare utilisation. In a retrospective study (30), extra-glandular damage – assessed using the SSDDI – conferred a higher risk of hospitalisation (OR 1.3, 95% CI 1.01–1.66). Renal damage (composite of CKD, persistent proteinuria, RTA, nephrocalcinosis, TIN, or GN) was linked to more frequent hospitalisations and a higher comorbidity burden over 10.4 years of follow-up (27).

Tooth loss was associated with decrements in selected QoL items in a large cross-sectional cohort (33), whereas joint erosions showed no association with HAQ in a smaller study (32). Global damage (SSDDI) correlated with the SF-36 general health domain in an earlier cross-sectional analysis (34). The data collectively emphasise the prognostic relevance of systemic damage in SjD and underline the importance of comprehensive damage assessment for guiding clinical management and improving patient outcomes.

Discussion

This systematic review provides a comprehensive synthesis of current evidence on the prevalence, determinants, and consequences of tissue and organ damage in SjD (Suppl. Fig. S1). Although SjD is classically viewed as a slowly progressive autoimmune condition with predominant exocrine manifestations, our findings highlight that irreversible damage is frequent, cumulative, and clinically meaningful, affecting both glandular and systemic domains.

Glandular involvement remains the hallmark and most prevalent clinical manifestation of SjD, accounting for the majority of irreversible organ damage observed in affected patients. In our review, across seven studies evaluating glandular involvement, salivary gland dysfunction was reported in 45–72% of patients, dental caries in 49–74.6%, and ocular damage in 25-64% of cases, reaching 76% when only structural ocular changes were considered. Oral damage assessed using the SSDI reached a prevalence of up to 86%. The association with persistent immunological activation, particularly elevated IgG, points to ongoing autoimmune processes driving glandular destruction. However, heterogeneity in assessment methods limits comparability and calls for standardisation of damage evaluation tools.

Systemic damage, particularly involving the renal and pulmonary systems, represents a key determinant of adverse outcomes in SjD. Multiple factors have consistently emerged as predictors of damage accrual. Advanced age and prolonged disease duration are repeatedly associated with both glandular and systemic involvement, underscoring the cumulative nature of tissue injury over time. Immunological parameters, including persistent hypergammaglobulinaemia, hypocomplementaemia (C3, C4), and anti-SSA/SSB positivity, have been identified as key correlates of progressive damage, suggesting that

sustained autoimmune activation and complement consumption may drive irreversible organ dysfunction. Notably, the absence of HCQ therapy has been linked to increased systemic damage, supporting a potential protective effect of antimalarial treatment, consistent with observations in other systemic autoimmune disorders.

Nevertheless, although heterogeneity in measures of damage evaluation and the predominance of retrospective study designs limit the ability to draw definitive conclusions regarding temporal causality, the collective evidence supports that damage accrual in SjD is multifactorial. It reflects an interplay of age-related vulnerability, persistent immune-mediated injury, and potentially suboptimal therapeutic intervention.

Notably, the present results highlighted that systemic damage substantially worsens survival and quality of life of SjD patients. Tooth loss correlates with lower oral-health QoL scores, whereas overall SSDDI scores are negatively associated with general health domains of the SF-36. Extra-glandular involvement, especially renal and pulmonary lesions, is linked to higher rates of hospitalisation, increased all-cause mortality, and greater comorbidity over long-term follow-up.

Collectively, these findings indicate that both cumulative damage and specific organ involvement, particularly in the pulmonary and renal systems, are associated with worse prognosis and greater healthcare utilisation, while also having a measurable impact on HRQoL. Of consequence, proper control of disease activity and awareness of specific organ involvement are of paramount importance to prevent or delay damage accrual in these patients.

The current evidence is, however, constrained by several limitations. First, there is heterogeneity in damage definitions and indices used across studies. While SSDDI and SSDI are validated, thresholds for damage accrual and attribution to SjD vary. Second, most studies were retrospective and had modest sample sizes, which may limit generalisability. Third, confounding by disease duration and treatment exposure was inconsistently addressed among studies, thus limiting the estimation of the impact of disease duration on damage and the long-term effects of treatment exposure. Finally, data on quality of life and patient-reported outcomes remain sparse, preventing quantitative meta-analysis.

Gaps in the literature and future research directions

Despite major advances in understanding SjD, important knowledge gaps persist regarding the mechanisms, assessment, and management of tissue and organ damage.

Firstly, heterogeneity of clinical phenotypes and disease trajectories continues to hinder the establishment of standardised definitions and validated metrics for irreversible damage across all ESSDAI domains. Instruments such as the SSDDI require additional validation in large, longitudinal, and ethnically diverse cohorts to ensure consistent assessment of cumulative damage (7, 10, 35). Additionally, the distinction between active inflammation and permanent damage remains difficult in clinical practice, limiting timely intervention.

The underlying molecular mechanisms of tissue remodelling and fibrosis are still incompletely characterised, and the contribution of novel immune subsets and non-immune pathways to chronic damage warrants further study (36). Reliable biomarkers capable of differentiating disease activity from established damage are still lacking, limiting patients' prognostic assessment and the implementation of precision medicine (9).

Therapeutically, while biologics and immunomodulatory agents have generated substantial expectation for better management of disease activity, robust evidence demonstrating their efficacy in preventing or reversing damage is limited.

Future research should prioritise longitudinal studies integrating multi-omics approaches, advanced imaging and patient-reported outcomes to develop comprehensive models of damage progression. Ultimately, these efforts will inform precision medicine strategies aimed at halting damage accumulation and improving quality of life for patients with SjD.

Conclusions

Cumulative glandular and systemic damage is frequent in SjD, affecting nearly half of patients after a decade of disease. Immunologic hyperactivity (high IgG, low complement), older age, sustained disease activity and lack of HCQ therapy are the most consistently reported factors associated with irreversible damage. Systemic damage, particularly in pulmonary and renal domains, contributes most to morbidity and mortality, while oral and ocular damage markedly impairs quality of life.

Early identification and prevention of irreversible organ injury should be integral to patient clinical management in SjD. Standardised use of validated damage indices and prospective longitudinal data will be crucial to understanding-and ultimately mitigating-damage accrual in this complex disease.

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