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Ophthalmic Outcomes Across CKD Stages in Systemic Lupus Erythematosus

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Abstract

Purpose: Systemic lupus erythematosus (SLE) carries renal and ocular morbidity. Chronic kidney disease (CKD) may worsen inflammatory and microvascular injury. This study evaluated whether CKD stage is associated with increased ophthalmic complications in SLE.

Methods: Adults with SLE in the TriNetX Research Network were stratified by CKD stage (1-5 and ESRD) and propensity-score matched 1:1 to SLE patients without CKD on age, sex, race, hypertension, diabetes mellitus, and other baseline variables. Patients with pre-existing ophthalmic diagnoses were excluded. Incident episcleritis, scleritis, cataract, hypertensive retinopathy, low vision, and blindness were assessed using risk ratios (RR) with 95% confidence intervals. Direct measures of lupus disease activity were not available in the database.

Results: Matched cohorts ranged from 5,500 to 28,000 patients. Inflammatory complications were elevated in early CKD: episcleritis (RR 1.54-1.94, stages 1-3) and scleritis (RR 1.43-2.08, stages 1-4). Cataract risk was increased across stages, highest in stage 1 (RR 1.75) and modestly elevated thereafter (RR 1.11-1.29). Hypertensive retinopathy demonstrated a clear severity gradient, rising from stage 1 (RR 1.56) to ESRD (RR 2.73). Vision-threatening outcomes also increased with CKD severity, with blindness peaking in ESRD (RR 2.28) and low vision elevated across all stages (RR 1.22-1.56).

Conclusions: Advancing CKD severity in SLE is associated with progressively higher inflammatory, vascular, and vision-threatening ophthalmic complications. These findings support CKD-stage-guided ophthalmic surveillance to reduce preventable vision loss.

Keywords: Systemic lupus erythematosus; Chronic kidney disease; Ophthalmic complications; Hypertensive retinopathy; Episcleritis; Scleritis; Vision loss; Microvascular disease.

Introduction

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease characterized by immune complex deposition, complement activation, and persistent systemic inflammation, with a strong predilection for women of childbearing age [1,2-8]. The disease can involve nearly every organ system, including the skin, joints, kidneys, cardiovascular system, lungs, eyes, and central nervous system [1,8]. Across these systems, microvascular injury represents a central pathogenic feature of SLE and is driven by immune complex-mediated endothelial dysfunction and inflammatory vasculopathy that may result in irreversible organ damage if not treated promptly [3,4].

Renal involvement, most commonly lupus nephritis, affects a substantial proportion of patients and remains a major contributor to long-term morbidity through

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Marina Z. Gad El Sayed, et al., J Opthalmol Res 2026
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progression to chronic kidney disease (CKD) [1,8]. Beyond its systemic consequences, CKD itself is characterized by chronic inflammation, endothelial dysfunction, metabolic disturbance, and hypertension-processes that may amplify microvascular injury in other organ systems, including the eye.

Ocular manifestations are reported in approximately one out of three patients with SLE and include a broad spectrum of anterior and posterior segment pathology [3,5,6,8]. Episcleritis and scleritis reflect immune-mediated inflammation of superficial and deep episcleral vessels and commonly present with ocular pain, redness, and photophobia [3,4,6]. Cataract formation, particularly posterior subcapsular cataracts, is also prevalent and is often associated with chronic corticosteroid use or intraocular inflammation [4,7,8]. In addition, hypertensive retinopathy may develop in the setting of systemic hypertension, which is common among patients with lupus nephritis and CKD, and may manifest as arteriolar narrowing, retinal hemorrhages, and cotton-wool spots [5,6,9,10]. When ocular involvement is progressive or unrecognized, visual consequences can be substantial, ranging from functional impairment to irreversible vision loss [3,5,8].

Independent of SLE, CKD is associated with microvascular dysfunction and an increased burden of retinal disease and visual impairment in the general population [9,11]. In patients with SLE, the coexistence of CKD may further amplify ocular vulnerability through overlapping mechanisms of chronic inflammation, endothelial injury, metabolic disturbance, and hypertension [3,9,11]. Recent optical coherence tomography angiography (OCT-A) studies have demonstrated reduced retinal capillary density and ischemic microvascular alterations in patients with lupus nephritis, with abnormalities correlating with renal disease severity [12,13]. Despite these observations, the extent to which CKD presence and severity independently modify the risk and patterns of ophthalmic complications in patients with SLE remains incompletely defined.

Accordingly, this study leverages a large real-world dataset and applies propensity score matching to evaluate whether chronic kidney disease stage modifies the risk of developing inflammatory, vascular, and vision-threatening ophthalmic outcomes in patients with SLE compared with matched SLE patients without CKD.

Methods

This retrospective cohort study was conducted using the TriNetX Research Network, a federated database of de-identified electronic health record data from multiple healthcare organizations, primarily within the United States. The database includes longitudinal demographic, diagnostic, and clinical information and is compliant with the Health Insurance Portability and Accountability Act. Because all data were de-identified, institutional review board approval was not required.

Adult patients aged 18 years or older with a diagnosis of systemic lupus erythematosus were identified using International Classification of Diseases, Tenth Revision diagnostic codes. Patients were stratified according to chronic kidney disease severity, including CKD stages 1 through 5 and end-stage renal disease. For each CKD stage, a corresponding comparator cohort of patients with systemic lupus erythematosus and no documented CKD was identified. Each CKD stage was analyzed independently to assess stage-specific associations.

The index date for patients with CKD was defined as the date of first documentation of the relevant CKD stage. For patients without CKD, a matched index date corresponding to the exposure cohort was assigned. Patients with documented ophthalmic outcomes of interest prior to the index date were excluded from analyses of those specific outcomes to ensure assessment of incident disease.

The primary exposure variable was CKD stage, categorized from stage 1 through stage 5 and ESRD. Ophthalmic outcomes included episcleritis, scleritis, cataract, hypertensive retinopathy, low vision, and blindness. Outcomes were identified using ICD-10 diagnostic codes recorded after the index date.

To reduce confounding, propensity score matching was performed separately for each CKD stage comparison using a one-to-one nearest-neighbor matching algorithm. Matching variables included age at index, sex, race and ethnicity, hypertension, diabetes mellitus, and hyperlipidemia. Covariate balance between cohorts was assessed using standardized mean differences and visual inspection of propensity score density plots. Post-matching standardized mean differences were generally below 0.1, indicating adequate balance.

Incident outcomes were compared between matched cohorts using risk ratios with corresponding 95% confidence intervals. Patients with outcomes documented prior to the analysis time window were excluded from the corresponding outcome analysis. All analyses were conducted within the TriNetX analytics platform.

Results

Across CKD stages, matched cohort sizes ranged from approximately 5,500 to 28,000 patients per group, depending on CKD severity. Prior to matching, patients with more advanced CKD were older and had higher prevalence of hypertension and diabetes compared with patients without CKD. After propensity score matching, baseline demographic and clinical characteristics were well balanced across all CKD stage comparisons.

Marina Z. Gad El Sayed, et al., J Opthalmol Res 2026
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In early CKD stages, inflammatory ocular complications predominated. Patients with CKD stages 1 and 2 demonstrated significantly higher risk of episcleritis and scleritis compared with matched patients without CKD. Episcleritis risk ratios ranged from approximately 1.5 to 1.9 in stages 1 through 3, while scleritis risk was elevated through stage 4, with risk ratios exceeding 1.4. Cataract risk was increased across all CKD stages, with the highest relative risk observed in CKD stage 1. Hypertensive retinopathy and low vision were modestly increased in early CKD but with smaller effect sizes than those observed in later stages (Figure 1).

In CKD stage 3, a transitional pattern of ocular risk emerged. Inflammatory outcomes such as episcleritis and scleritis remained elevated but with attenuated effect sizes compared to earlier stages. Cataract risk continued to be significantly increased. In contrast, hypertensive retinopathy demonstrated a more pronounced association, indicating the emergence of vascular-mediated retinal pathology. Low vision risk was also higher in stage 3 compared with earlier stages (Figure 1).

In advanced CKD stages, vascular and vision-threatening outcomes became the dominant features. In CKD stages 4 and 5, inflammatory ocular complications were less prominent, while hypertensive retinopathy showed strong and consistent associations. Cataract risk remained elevated with relatively stable effect sizes. Low vision was significantly increased, reflecting clinically meaningful visual impairment associated with advanced renal dysfunction (Figure 1).

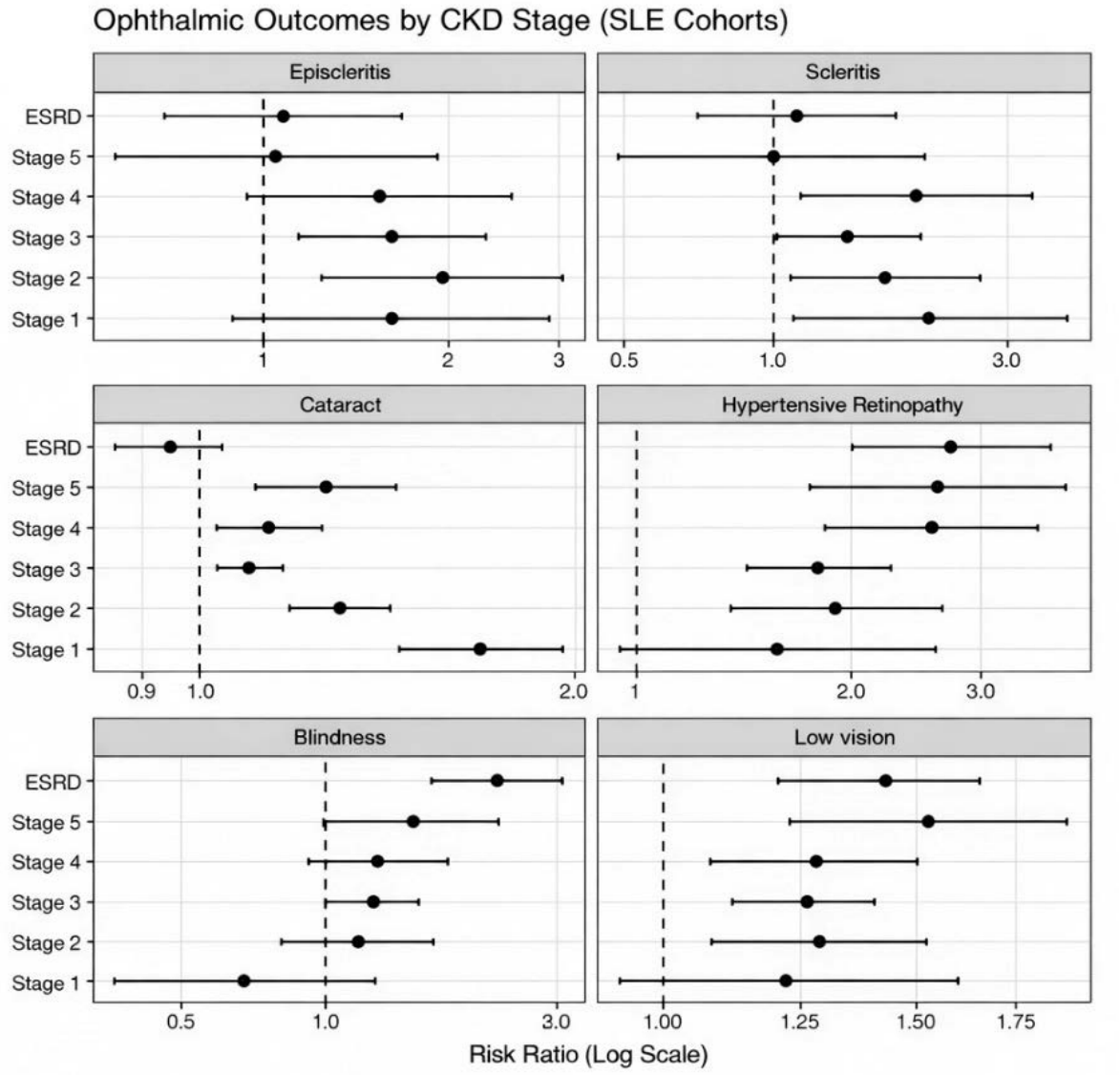

Figure 1: Risk ratios for inflammatory and vision-related ophthalmic outcomes across CKD stages in systemic lupus erythematosus. Values are derived from 1:1 propensity score–matched analyses versus patients without CKD (95% CI shown). The dashed line marks a risk ratio of 1.0; ESRD denotes end-stage renal disease.

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Among patients with end-stage renal disease, the strongest associations were observed. Hypertensive retinopathy risk exceeded a risk ratio of 2.5, representing the most pronounced effect across all stages. Blindness risk was highest in ESRD, with risk ratios exceeding 2.0. Low vision remained significantly elevated, indicating cumulative and severe ocular morbidity in this population (Figure 1).

Across all analyses, a clear severity-dependent gradient was observed (Supplementary Figure S1). Early CKD stages were characterized primarily by inflammatory ocular disease and cataracts, moderate CKD by mixed inflammatory and vascular pathology, and advanced CKD and ESRD by vascular retinopathy and vision-threatening outcomes. This pattern was consistent across all matched cohorts and outcome measures.

Discussion

In this large, real-world cohort of patients with systemic lupus erythematosus, chronic kidney disease was associated with substantially increased burden of ophthalmic morbidity, with distinct stage-dependent patterns of ocular involvement. After adjustment for demographic factors and major systemic comorbidities through propensity score matched, patients with SLE and CKD demonstrated increased risks of inflammatory ocular disease, cataract formation, retinal vascular pathology, and vision-compromising outcomes when compared with matched SLE patients without CKD.

Inflammatory ocular complications were most prominent in the early stages of CKD. Elevated risks of episcleritic and scleritis in mild CKD likely reflect persistent immune-mediated vascular injury affected highly vascularized ocular tissues. Ongoing immune complex deposition, complement activation, and systemic inflammation characteristic of SLE and early renal disease provide a biologically plausible explanation for the predominance of inflammatory ocular findings. Cataract risk was also elevated in early CKD, potentially reflecting cumulative corticosteroid exposure, sustained inflammation, and metabolic disturbances associated with renal dysfunction rather than progressive vascular injury.

CKD stage 3 appeared to represent a transitional phase in which inflammatory ocular disease persisted while vascular pathology became increasingly evident. This rising association with hypertensive retinopathy and low vision at this stage likely reflects the growing contribution of endothelial dysfunction and hypertension as renal function declines.

In the advanced stages of CKD (4-5), there is less inflammatory eye disease but an increase in hypertensive retinopathy, demonstrating the elevated prominence of vascular damage. In these stages, severe kidney disease causes high blood pressure and microvascular injury characterized by the narrowing of retinal blood vessels and ischemic alterations evident in hypertensive retinopathy. Although cataract risk remained elevated, effect sizes were relatively stable across stages, supporting the interpretation that cataract development in SLE is more closely related to chronic inflammation and corticosteroid exposure than to CKD severity alone.

Among patients with ERSD, the highest risks of hypertensive retinopathy, low vision, and blindness were observed. These findings likely reflect cumulative microvascular injury, chronic retinal ischemia, and potential delays in ophthalmic detection or intervention in patients with advanced systemic disease. At this stage, the kidneys have failed, causing severe high blood pressure and systemic vascular damage.

Collectively, these findings demonstrate a clear stage-dependent evolution of ocular risk in SLE patients with CKD. Early CKD stages are dominated by inflammatory ocular manifestations, intermediate stages by a transition from inflammation to vascular pathology, advanced stages by vascular injury, and end-stage renal disease by the highest risk of hypertensive retinopathy and irreversible vision loss. These results underscore the importance of CKD-stage-guided ophthalmic surveillance in SLE, with emphasis on early detection of inflammatory disease in mild CKD, heightened monitoring for vascular retinal pathology in moderate CKD, and aggressive vision-preserving strategies in advanced CKD and ESRD.

Strengths and Limitations

Strengths of this study include its large, real-world sample of patients with systemic lupus erythematosus derived from a multi-institutional electronic health record database, enabling for evaluation of uncommon ophthalmic outcomes. Stratification by CKD stage allowed for assessment of severity-dependent risk patterns, and propensity score matching strengthened comparisons between patients with and without CKD. The incorporation of a broad spectrum of ophthalmic outcomes allows for a wider analysis of ophthalmic conditions in those with SLE. The consistent outcomes throughout CKD stages also highlight biological plausibility in these conditions.

Limitations include reliance on ICD-10 diagnostic codes, which may lead to misclassification of SLE, CKD stage, or ophthalmic outcomes. Direct measures of SLE disease were unavailable. Medication exposure was not directly analyzed and may represent an unmeasured source of confounding. Unmeasured factors such as smoking status and socioeconomic determinants may also have influenced outcomes. Finally, the cohort may preferentially represent patients with consistent access to healthcare, potentially limiting generalizability to underrepresented populations.

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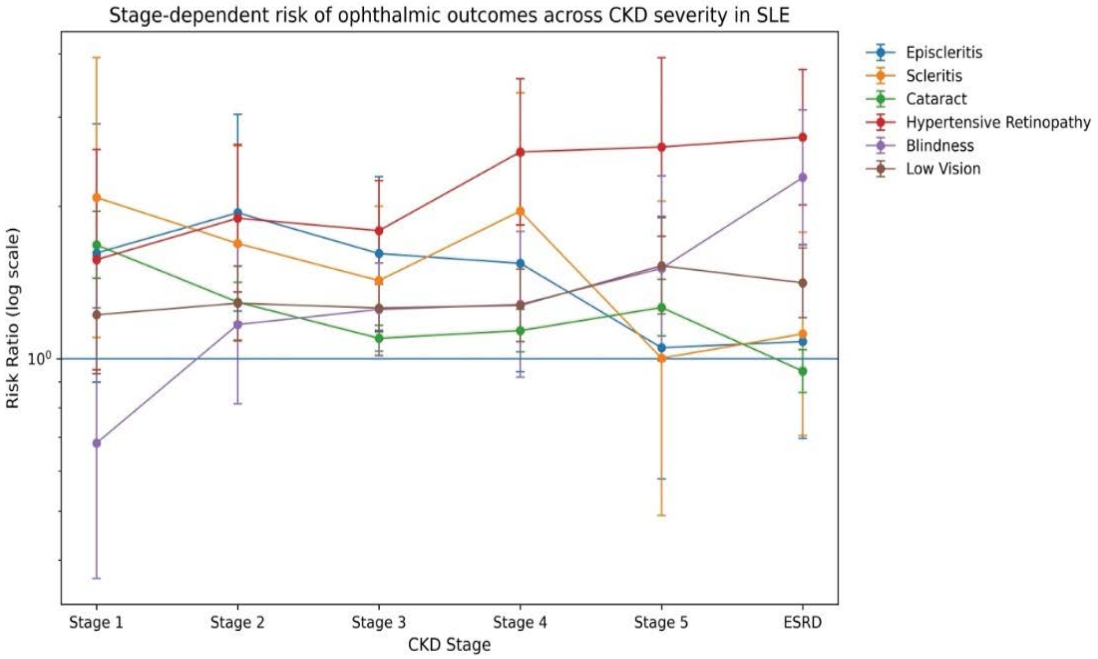

Supplementary Figure S1: Stage-dependent risk of ophthalmic outcomes across CKD severity in systemic lupus erythematosus. Points represent risk ratios and error bars indicate 95% confidence intervals plotted on a logarithmic scale.