Identifying Risk Factors of Flare(s) in Patients With SLE After Glucocorticoid Withdrawal (<7.5mg/day) Across 1.5-Years

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OBJECTIVE

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by unpredictable flare-ups that can lead to irreversible organ damage and diminished quality of life. Glucocorticoids are a cornerstone in managing disease activity but carry significant long-term side effects. Identifying risk factors for flares following glucocorticoid withdrawal is critical to balancing disease control and treatment burden[1][2]. This study aims to explore the relationship between glucocorticoid withdrawal strategies and long-term harm.

METHODOLOGY

Longitudinal data from the FORWARD Lupus Registry (1999–2024) were analyzed. A total of 1085 participants completed at least three consecutive questionnaires approximately six months apart. From this cohort, 209 patients with glucocorticoid withdrawal (<7.5mg/day) after prior use were identified based on tracked medication change. After excluding patients with missing values on relevant variables, a final set of 95 patients was retained, and all their multiple follow-up records were used for model fittings.

Covariates were included in the prediction model: Age, BMI, PHQ-8 Score, Global Severity, Sex, Diabetes, Allergies, Medicare Status, Current Cancer, and Renal Disease. Flare risk was assessed using a Generalized Linear Mixed Model (GLMM) with patient-level random intercepts to account for repeated measures. Two models were compared: a baseline model incorporating linear terms for all predictors, and a nonlinear model utilizing natural splines for continuous variables (Age, BMI, PHQ-8 Score, and Global Severity). Model performance was evaluated using likelihood ratio testing, area under the curve (AUC), and calibration plots.

RESULTS

Table 1. Descriptive Statistics by Flare Occurrence
No flare vs. Flare during follow up

Values are presented as *mean ± standard deviations* on Continuous Variables; *percentages* on Categorical Variables

	Overall (N = 95)	No Flare (n = 9)	Flare (n = 86)
Age (years)	61.76 ± 13.46	63.30 ± 15.09	61.60 ± 13.36
Body Mass Index (BMI)	28.16 ± 6.9	27.39 ± 9.87	28.24 ± 6.59
PHQ-8 Score*	6.00 ± 3.93	2.23 ± 1.88	6.39 ± 3.88
Global Severity*	4.23 ± 1.78	2.70 ± 1.78	4.39 ± 1.71
Sex			
Female	95.79	100	95.35
Male	4.21	0	4.65
Diabetes			
Yes	15.79	22.22	15.12
No	84.21	77.78	84.88
Allergies			
Yes	44.21	33.33	45.35
No	55.79	66.67	54.65
Medicare Insurance			
Yes	75.79	77.78	75.58
No	24.21	22.22	24.42
Current Cancer			
Yes	20.00	22.22	19.77
No	80.00	77.78	80.23
Renal Disease			
Yes	44.21	22.22	46.51
No	55.79	77.78	55.79

* **PHQ-8 Score:** Measures depressive symptoms based on the Patient Health Questionnaire-8.
* **Global Severity:** Assesses the overall intensity of a condition or symptoms, combining multiple clinical factors into a single measure.

Table 1. Descriptive statistics summarize demographic and clinical characteristics by flare status (flare and no flare) after glucocorticoid withdrawal. Compared to patients without flares, those who experienced flares showed higher levels of depressive symptoms and global severity scores, and a greater prevalence of renal disease and allergies.

To establish a baseline, a generalized linear mixed model (GLMM) was first fitted using key demographic and clinical predictors without modeling non-linear effects. This model included age, sex, BMI, PHQ-8, comorbidities, and insurance status, with a random intercept for each patient. The model achieved an AUC of 0.909, indicating good discrimination between flare and non-flare outcomes. However, residual analysis and visual inspections suggested potential non-linear relationships for continuous variables.

Figure 1. Natural Splines of Continuous Variables on Risk of Post-Withdrawal Flare

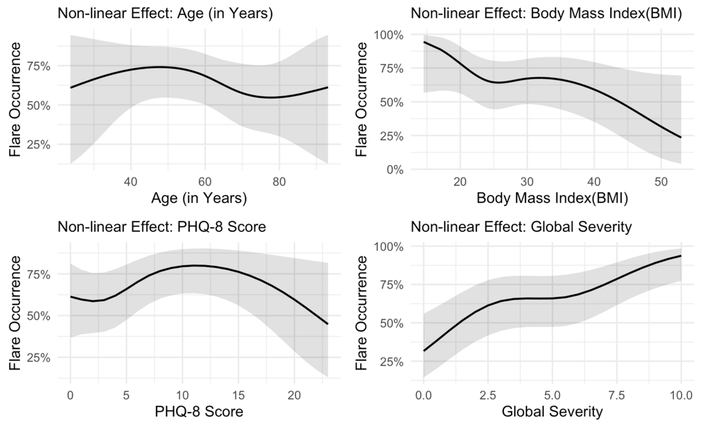

Figure 1 illustrates the estimated probability of post-withdrawal flare across the range of each continuous predictor, modeled using natural splines to capture non-linear trends. Shaded bands indicate 95% confidence intervals, highlighting uncertainty across the predictor range.

Flare risk varied meaningfully with patient characteristics:

- **Age** showed a non-linear trend, with higher risk before 50, a dip between 50–70, and a rise again at older age.
- **BMI** was inversely related to flare probability, especially at lower levels, with the effect plateauing at higher BMI.
- **PHQ-8 scores** were associated with increasing risk up to a moderate level, then slightly declining beyond that.
- **Global Severity** demonstrated a strong, nearly linear increase in flare risk — one of the most influential predictors.

These patterns highlight the value of flexible modeling, offering a more personalized view of flare risk compared to traditional linear models.

Figure 2. ROC Curve (AUC = 0.913) for the Nonlinear GLMM Predicting Flare Risk

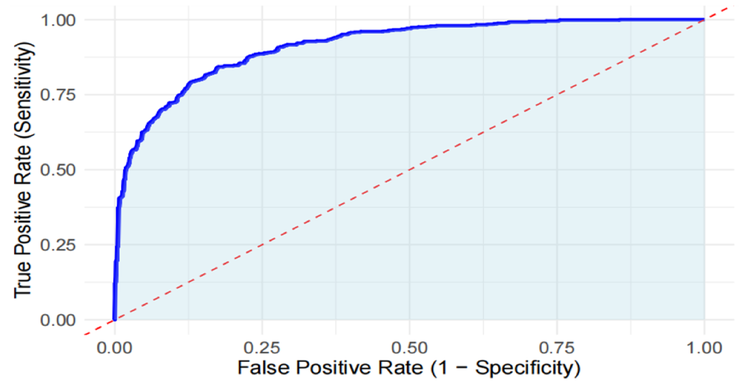

Figure 2 presents the ROC curve for the nonlinear generalized linear mixed model (GLMM) predicting flare risk after glucocorticoid withdrawal. The curve demonstrates the model's ability to discriminate between flare and non-flare occurrences, with an area under the curve (AUC) of 0.913, indicating strong predictive accuracy.

The figure highlights the improved model fit achieved by introducing natural splines for continuous predictors such as Age, BMI, PHQ-8 Score, and Global Severity. The nonlinear model outperformed the baseline model, as indicated by a statistically significant improvement in fit ($p = 0.02$), while maintaining interpretability. These results underscore the model's enhanced clinical relevance and calibration in predicting patient-specific flare risk.

CONCLUSION

After glucocorticoid discontinuation or dose reduction, flare risk in SLE patients was associated with higher disease occurrence, depressive symptoms, diabetes, and allergies, while Medicare coverage and higher BMI levels (with nonlinear effects) appeared protective. Using a flexible mixed-effects model with splines captured how these risk factors vary across clinical gradients, highlighting the importance of personalized monitoring and targeted interventions during the post-treatment period.

REFERENCES

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