



Risk factors of flare in patients with systemic lupus erythematosus after glucocorticoids withdrawal. A systematic review and meta-analysis

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ABSTRACT

Objective Glucocorticoids (GC) withdrawal is part of the targets in current recommendations for SLE, but relapse is the most worrying issue. We aimed to investigate the predictors for flare in patients with SLE after GC withdrawal.

Methods We systematically searched PubMed, EMBASE and Cochrane Library as well as Scopus databases up to 9 July 2021 for studies concerning predictive factors of relapses in patients with SLE after GC cessation. Pooled OR and 95% CI were combined using a random-effects or fixed-effects model.

Results 635 patients with SLE with GC discontinuation in 9 publications were eligible for the final analysis. Of them, 99.5% patients were in clinical remission before GC withdrawal. Serologically active yet clinically quiescent (SACQ) was associated with an increased risk of flare after GC withdrawal (OR 1.78, 95% CI (1.00 to 3.15)). Older age and concomitant use of hydroxychloroquine (HCQ) trended towards decreased risk of flare (weighted mean difference (WMD) -2.04 , 95% CI $(-4.15$ to $0.06)$ for age and OR 0.50, 95% CI (0.23 to 1.07) for HCQ), yet not statistically significant. No significant association was observed regarding gender (pooled OR 1.75; 95% CI (0.59 to 5.20)), disease duration (WMD -11.91 , 95% CI $(-27.73$ to $3.91)$), remission duration (WMD -8.55 , 95% CI $(-33.33$ to $16.23)$), GC treatment duration (WMD -10.10 , 95% CI $(-64.09$ to $43.88)$), concomitant use of immunosuppressant (OR 0.86, 95% CI (0.48 to 1.53)).

Conclusion Younger age and SACQ were potential risk factors of SLE flare among patients who discontinued GC. HCQ, but not immunosuppressant might prevent flare. GC withdrawal should be done with caution in this subgroup of patients.

INTRODUCTION

Glucocorticoids (GC) have been the cornerstone in the treatment of SLE, irrespective of immunosuppressive agents or biological therapy. Nevertheless, prolonged use of GC may cause irreversible organ damage, leading to impaired quality of life and even increased mortality. Risks are substantially increased at a maintenance doses of prednisone >7.5 mg/day or equivalent, while some studies

Key messages

What is already known about this subject?

- Glucocorticoids (GC) have been the cornerstone in the treatment of SLE.
- Prolonged use of GC may cause irreversible organ damage; however, GC discontinuation might lead to an increased risk of flare.

What does this study add?

- In this meta-analysis, we found younger age and serologically active clinically quiescent were potential risk factors of SLE flare among patients who discontinued GC.
- Hydroxychloroquine might prevent flare among these patients.

How might this impact on clinical practice or future developments?

- Our findings can help physicians to identify those patients with SLE who may successfully discontinue GC; this may also facilitate further clinical studies of GC withdrawal.

suggested that lower doses of GC might also be harmful.¹⁻⁶ Accordingly, two recent European League Against Rheumatism recommendations for SLE and lupus nephritis (LN) indicated that GC should be the first drug, when possible, to be withdrawn during the maintenance period.^{7,8} However, no specific guidelines advising baseline screening of candidate patients for GC discontinuation has been ever proposed so far. Our recent meta-analysis has shown that GC discontinuation leads to a statistically significant increased risk of flare (relative risk (RR) 1.38, 95% CI (1.01 to 1.89)) and 54.2% of the flares were severe flares.⁹ Nevertheless, a trend of risk reduction in further organ damage can be observed in patients who discontinued GC. Therefore, it is still worthy trying to discontinue GC in patients with SLE, but careful selection of candidates to GC withdrawal is mandatory.

In the past decades, some demographics-related, disease-related and therapy-related factors have been proposed for predicting flare. Nevertheless, the conclusions remain limited and contradictory, confusing.^{10 11} To date, no comprehensive meta-analysis on predictive factors for SLE flare after GC withdrawal has been conducted. To fill the gap, we performed this systematic review and meta-analysis of the published literature to identify possible predictors of disease flare among patients with SLE after GC cessation.

METHODS

The systematic review protocol and data extraction forms were designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Patient and public involvement was not applicable.

Literature search and inclusion criteria

Literature search was performed in Medline/PubMed, EMBASE, the Cochrane Library databases and Scopus from inception to 9 July 2021 without language restrictions, adhering to the principles of comprehensive bibliographic searches. Our search strategy combined the use of four separate search strings (see online supplemental data S1). The first string was designed to capture

all studies in SLE. The second and third strings were designed to include all the studies on GC withdrawal. The last string was designed to find the studies providing data regarding flare. In addition, reference lists from included studies and abstracts of scientific meetings from American College of Rheumatology and European League against Rheumatism (2015–2020) were screened for potential eligible reports.

The article inclusion criteria applied to the title and abstract reading were: (1) studies in patients with SLE; (2) randomised controlled trials (RCTs) or cohort studies; (3) reporting at least one risk factor for flare after GC withdrawal; (4) presenting HRs (or RRs or ORs) with 95% CIs or the data necessary to calculate them. Exclusion criteria consisted of (1) patients in pregnancy; (2) patients receiving stem cell transplantation; (3) patients with other conditions that may impact GC withdrawal, such as inflammatory arthropathy, inflammatory myopathy. Flare was recorded according to what was mentioned in the studies. For studies of duplicate or overlapping patient populations, the article with more complete information or articles concerning different outcomes were retained. There were no restrictions with regard to age, race/ethnicity, gender or concomitant treatment. Two authors (LJ and WX) independently reviewed the potential titles,

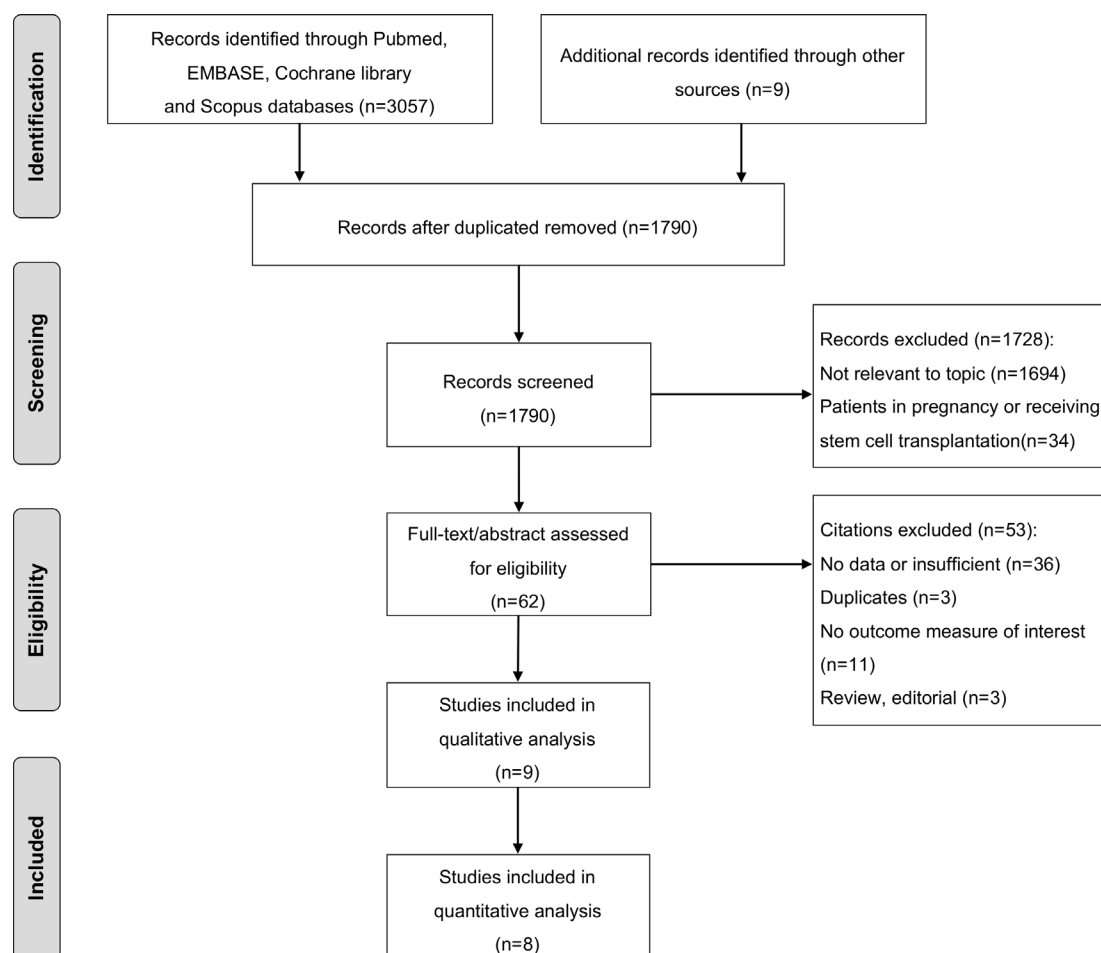


Figure 1 The flow chart of study selection.

Table 1 The characteristics of published articles concerning risk factors of flare selected for the systemic review and meta-analysis

Study, country (design)	Flare/ Non-flare numbers	Risk factors, effect size (95%CI)		SACQ	Treatment	Other risk factors
		Age	Female			
Fasano <i>et al.</i> , ²¹ Italy (cohort)	9/47	HR 0.97 (0.93 to 1.02); WMD: -2.59 (-4.15 to 0.06)	/	HR 2.99 (1.08 to 8.25)* hypocomplementaemia: HR 25.97 (3.12 to 216.18) anti- dsDNA: HR 1.03 (1.01 to 1.07)	HCQ: HR 1.62 (0.19 to 13.46); duration of HCQ: HR 0.84 (0.72 to 0.98); IS: HR 2.39 (0.86 to 6.62)	Disease duration: HR 1.01 (0.92 to 1.10); WMD -3.00 (-61.12 to 55.12) Remission duration: WMD -15.84 (-34.46 to 2.78) 5-year remission: HR 0.12 (0.04 to 0.39) GC duration: WMD -18.36 (-77.67 to 40.95) LN: HR 3.38 (1.22 to 9.33) SDI score: HR 1.13 (0.63 to 2.01)
Mathian <i>et al.</i> , ²⁰ France (RCT)	17/46	/	OR 6.65 (0.36 to 123)	Low C3: OR 0.70 (0.195 to 2.541) anti-dsDNA: OR 1.16 (0.38 to 3.53)	HCQ: OR 0.44 (0.09 to 2.23); IS: OR 0.87 (0.24 to 3.20)	/
Tselios <i>et al.</i> , ²³ Canada (cohort) abstract	12/102	/	/	/	IS at baseline: HR 0.64 (0.44 to 0.94)	/
Tani <i>et al.</i> , ¹⁹ Italy (cohort)	18/59	/	/	Clinical remission (not complete remission): OR 0.53 (0.16 to 1.79)	HCQ: OR 0.89 (0.27 to 2.90); IS: OR 0.56 (0.18 to 1.78); biologics: OR 0.33 (0.02 to 6.49)	Disease duration: OR 1.01 (0.94 to 1.07) Remission duration: aOR 0.8 (0.64 to 1.8) Complete remission: OR 0.73 (0.25 to 2.18) LLDAS: OR 4.47 (0.89 to 22.4) SLEDAI: aOR 1.11 (0.72 to 1.00) SDI score 0.45 (0.10 to 1.86)
Goswami <i>et al.</i> , ¹⁸ India (cohort)	31/117	aHR 1.00 (0.98 to 1.02); WMD -3.60 (-6.78 to 0.42)	HR 0.85 (0.54 to 1.33)	HR 1.18 (0.72 to 1.94)	IS: aHR 0.53 (0.35 to 0.80)	Disease duration: aHR 1.12 (1.06 to 1.19) GC duration: aHR 1.00 (1.00 to 1.00) Myositis: aHR 1.23 (0.24 to 1.25) NP-SLE: aHR 0.96 (0.47 to 1.96) Thrombocytopenia: aHR 0.79 (0.31 to 2.04) vasculitis: HR 1.00 (0.31 to 3.12) Arthritis: HR 0.65 (0.31 to 1.33) Mucocutaneous: HR 0.92 (0.62 to 1.37) Serositis: HR 0.85 (0.45 to 1.64) LN: HR 0.94 (0.65 to 1.37) SDI >0: HR 1.30 (0.78 to 2.15)
Nalotto <i>et al.</i> , ²² Italy (cohort) abstract	22/82	WMD -1.14 (-6.23 to 3.95)	OR 8.74 (0.50 to 153)	aOR 3.17 (0.37 to 27.0)	IS: OR 1.08 (0.42 to 2.82)	Disease duration: WMD 4.39 (-49.48 to 58.26) GC duration: WMD 12.39 (-32.11 to 56.89) Remission duration: WMD -6.33 (-18.56 to 5.90) Mucocutaneous: aOR 3.07 (1.11 to 8.53) Arthritis: aOR 2.75 (0.80 to 9.44) Haematological involvement: aOR 1.89 (0.62 to 5.73) Vasculitis: OR 1.95 (0.33 to 11.4) Serositis: OR 0.84 (0.22 to 3.25) LN: OR 0.66 (0.25 to 1.70) NP-SLE: OR 0.92 (0.18 to 4.70) SDI >3: OR 0.92 (0.18 to 4.70)

Continued

Table 1 Continued

Study, country (design)	Flare/ Non-flare numbers	Risk factors, effect size (95% CI)			SACQ	Treatment	Other risk factors
		Age	Female	Chloroquine			
Moroni <i>et al.</i> , ¹⁷ Italy (cohort)	20/32	WMD -0.30 (-4.54 to 3.94)	OR 0.60 (0.08 to 4.64)	anti-dsDNA: OR 0.56 (0.16 to 1.92) low C3: OR 1.92 (0.55 to 6.67) low C4: OR 0.94 (0.28 to 3.17)	Chloroquine: 0.10 (0.02 to 0.49)	GC duration: WMD -67.10 (-95.32 to -38.88) Remission duration: WMD -40.80 (-57.93 to -23.67)	
Arnal <i>et al.</i> , ¹⁶ France (cohort)	3/7	/	/	/	/	GC duration: WMD 34.30 (1.72 to 66.88)	
Euler <i>et al.</i> , ¹⁵ Germany (cohort)†	3/8	WMD 3.00 (-8.74 to 14.74)	/	/	/	Disease duration: WMD -56.13 (-79.08 to -33.17)	

If available, we extracted the risk estimates that were adjusted for the most variables. When no raw data were available, HRs were taken as good estimates of ORs.

*The HR value of SACQ in Fasano, 2021 seems to have some mistakes, so we used the HR value.²⁴

†These patients received three consecutive plasmaphereses, followed by very high-dose cyclophosphamide pulse therapy in the initial stage. One patient was excluded because she died from sequelae of the liver cirrhosis during the follow-up.

./, not available; aHR, adjusted HR; aOR, adjusted OR; dsDNA, double-stranded DNA; GC, glucocorticoids; HCQ, hydroxychloroquine; IS, immunosuppressant; LLDAS, low lupus disease activity score; LN, lupus nephritis; NP, neuropsychiatric; RCT, randomised controlled trial; SACQ, serologically active clinically quiescent; SDI, Systemic Lupus International Collaborating Clinics Damage Index; SLEDAI, SLE Disease Activity Index; WMD, weighted mean difference.

abstracts and/or full manuscripts to evaluate the eligibility of studies. Any disagreement was resolved by the third experienced reviewer (ZZ).

Data extraction and study quality assessment

Data extraction of eligible studies was conducted by two independent review authors (LJ and WX) using a predefined standardised grid. Extracted data included the following: author, year of publication, country, study design, data source, setting, enrolment period, sample size, demographics and clinical characteristics, outcomes of interest. In the case of data missing, the corresponding authors of the article were contacted by email.

Two investigators (LJ and WX) independently evaluated the quality of selected studies using the Cochrane Handbook bias risk assessment tool for RCTs¹² and Newcastle-Ottawa Scale for cohort studies,¹³ respectively. The details are available in online supplemental table S1 and S2.

Data synthesis and analysis

We calculated pooled risk ratio (OR) with 95% CIs for dichotomous outcomes and weighted mean difference (WMD) with 95% CI for continuous outcomes. The risk estimates adjusted for the most variables were extracted when available. If raw data were unavailable, HRs were taken as good estimates of ORs, in line with previous report.¹⁴ Heterogeneity across studies was measured by I^2 statistics. When insignificant heterogeneity with $I^2 \leq 50\%$ was present, the fixed-effects model (Mantel-Haenszel method) was used to estimate the effect value, while the random-effects model (DerSimonian and Laird method) was used when $I^2 > 50\%$ indicating significant heterogeneity. A funnel plot was used to qualitatively assess the quality of the articles. Begg's rank correlation and Egger's regression tests were used for quantitative evaluation of publication bias. For statistical significance, two-sided α was set at $p < 0.05$. All data were recorded in a Microsoft Excel spreadsheet and further analysed using STATA V.13.

RESULTS

Study selection and characteristics

The systematic search retrieved 3057 titles and 9 additional titles from the reference lists and abstracts of scientific meetings. After duplicates were removed, there were 1790 potentially relevant articles. Based on title and abstract, 62 were chosen for full-text review and further assessed for eligibility. Finally, a total of 9 citations (7 articles¹⁵⁻²¹ and 2 abstracts^{22,23}) comprising 635 patients with SLE who discontinued GC were eligible for the final analysis (figure 1). Of these, 632 (99.5%) patients were in clinical remission (clinical SLE Disease Activity Index=0) before GC withdrawal. Three patients with partial remission was defined as platelets count $50-150 \times 10^9/L$ in one study¹⁶ and they were only included in the analysis of flare after GC discontinuation regarding GC duration. The mean disease duration ranged from 48 to 188 months. The mean duration of remission before GC withdrawal

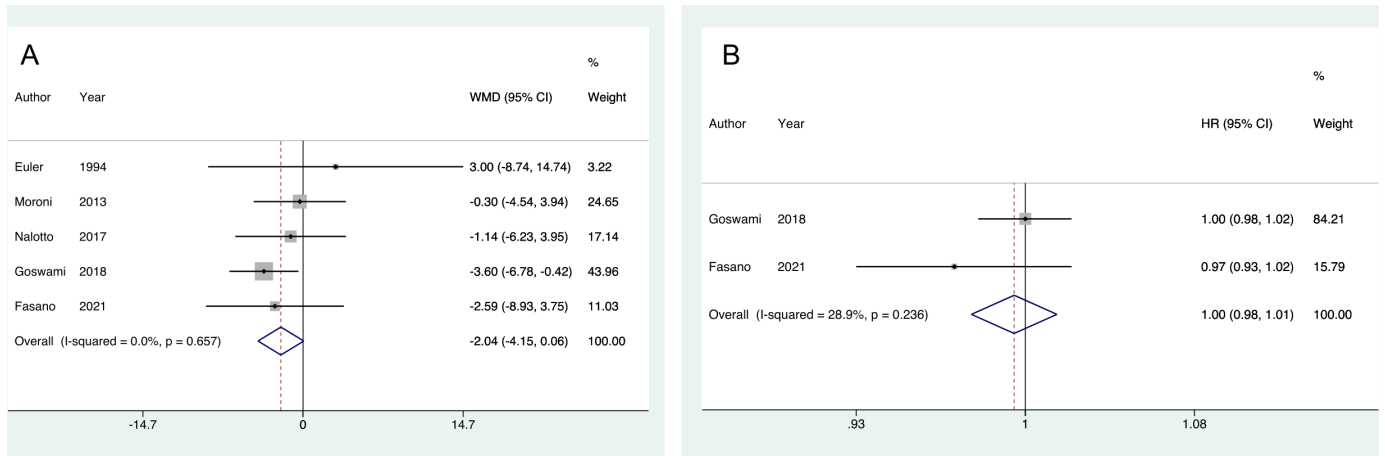


Figure 2 Forest plots of the weighted mean difference (WMD) and HR for the risk of flare in patients who stopped glucocorticoids regarding age: (A) WMD for continuous measurement; (B) HR for dichotomous measurement.

varied from 3 to 68 months. Only four studies mentioned the baseline GC dosage as 5 mg/day, requiring 0.25–24 months to complete withdrawal^{15 19 20 23}; 21.4% (135/632) patients flared after GC cessation, during a mean follow-up of 17.8–286 months. The study designs and characteristics are summarised in [table 1](#).

Age

The association between age and disease flare in patients with SLE after GC cessation was assessed by five articles with a median quality score of 8 (range 6–9).^{15 17 18 22 24} Of these, 371 patients were included and 85 (22.9%) of them flared after GC cessation. The mean age ranged from 29 to 39 years. The pooled WMD was -2.04 (95% CI -4.15 to 0.06 ; $I^2=0.0\%$) years ([figure 2A](#)). Subgroup analysis of two studies providing HR value of age found that the pooled HR of age was 1.00 (95% CI 0.98 to 1.01; $I^2=28.9\%$) ([figure 2B](#)).

Gender

Our meta-analysis of gender included 4 studies involving 367 patients who stopped GC with a median quality score of 8 (range 6–9)^{17 18 20 22}; 94.0% (345/367) of them were female. [Figure 3](#) summarises the pooled results of studies,

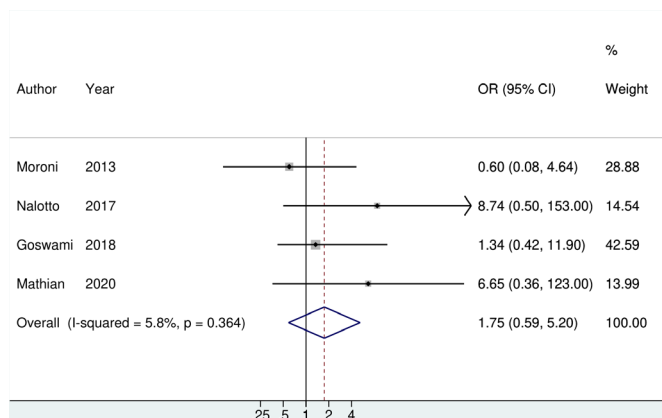


Figure 3 Forest plots of the OR for the risk of flare in patients who stopped glucocorticoids regarding gender.

showing a trend of increased flare risk of female after GC withdrawal, however statistically insignificant (pooled OR 1.75; 95% CI 0.59 to 5.20; $I^2=5.8\%$).

Serologically active clinically quiescent

The risk of flare after GC cessation with regard to serologically active clinically quiescent (SACQ) was investigated in a total of 4 studies comprising 385 patients with SLE.^{18 19 22 24} The median quality score of the 4 studies was 7.5, ranging from 6 to 9. In pooled analysis, SACQ was associated with an increased risk of flare (pooled OR=1.78; 95% CI 1.00 to 3.15) ([figure 4](#)).

Major organ involvement

Only 3 studies involving 309 patients with SLE evaluated the association between LN and disease flare after GC withdrawal.^{18 22 24} The quality scores were between 6 and 9. There was no significant association between LN and disease flare (pooled OR 1.20; 95% CI 0.55 to 2.64) (online supplemental figure S1A). There were 2 studies involving 252 patients with SLE investigating neuropsychiatric (NP)-SLE.^{18 22} No significant association was detected between NP-SLE and disease flare (pooled OR

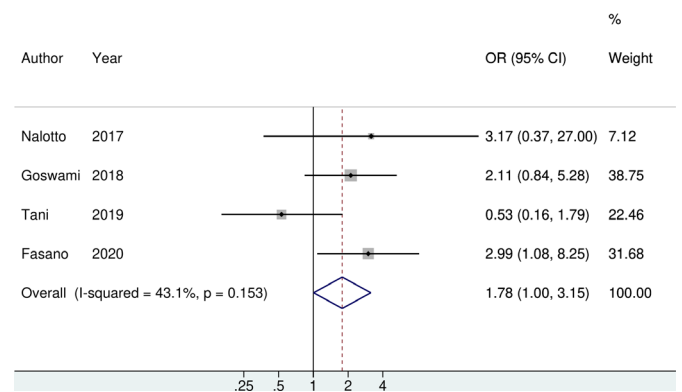


Figure 4 Forest plots of the OR for the risk of flare in patients who stopped glucocorticoids regarding serologically active clinically quiescent.



Figure 5 Forest plots of the OR for the risk of flare in patients who stopped glucocorticoids regarding concomitant treatment: (A) hydroxychloroquine; (B) immunosuppressant.

0.95; 95% CI 0.50 to 1.83) (online supplemental figure S1B).

Treatment

The association of treatment with flare was investigated in 448 patients with SLE from 5 studies, with a median quality score of 8 (range 6–9).^{17–20 24} There was a trend of decreased risk of flare regarding HCQ usage (pooled OR 0.50; 95% CI 0.23 to 1.07), although it did not reach statistical significance (figure 5A). Regarding immunosuppressant (IS), no significant association was detected (pooled OR 0.86; 95% CI 0.48 to 1.53) (figure 5B).

Other factors

No significant associations were observed for disease duration (pooled WMD –20.7 (95% CI –52.3 to 10.9)),^{15 18 22 24} remission duration before GC discontinuation (pooled WMD –8.55 (95% CI –33.3 to 16.2))^{17 19 22 24} and GC treatment duration (pooled WMD –10.1 (95% CI –64.1 to 43.9))^{16 17 22 24} (online supplemental figure S2–S4).

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis which assessed the predictive factors of lupus flare after GC withdrawal. According to our results, SACQ was a risk factor of disease flare among patients with SLE after GC cessation. Older age and HCQ usage trended towards decreasing the likelihood of flare.

GC withdrawal could be a reasonable goal to target for both physicians and patients with lupus. GC has been listed as the first drug to be withdrawn during maintenance stage in recent global recommendations.^{7 8} But currently several questions are left to the physicians, for instance, who may successfully discontinue GC. So, we analysed the potential factors which might predict lupus flare when patients stopped GC.

Demographically, younger patients were more likely to experience disease flare. Oestrogen contributes to the pathogenesis of SLE and younger age at disease onset has been known to be associated with more severe disease,

accrual damage and death.^{8 25} Our results confirmed that patients who flared were 2 years younger than those who did not flare. But unfortunately, we could not find the differential risk of premenopausal and postmenopausal flare based on insufficient data. Further study evaluating the predictive value of menopause would be more instructive for clinical practice.

In disease-related variables, patients with SACQ had an increased risk of flare. There was a subset of patients with SLE with fluctuating immunological abnormalities, including positive anti-dsDNA and hypocomplementaemia, however clinically inactive over a long period of time. There is general agreement that the presence of serological activity per se is not an indication for more intensive treatment in SLE.^{26 27} But both positive anti-dsDNA and hypocomplementaemia have been shown to be associated with global and renal flares,^{8 25} even the tendency of decline in serum complements should also be considered as the risk factors for flare.²¹ Although intensified treatment is unnecessary, tight surveillance is warranted and treatment de-escalation should be done with caution in this subgroup of patients with SACQ.

Regarding major organ involvement, renal, neurological and vasculitic involvement has been reported as independent predictors of flare in several studies.^{28 29} Unfortunately, we did not find any significant association between LN and disease flare, nor did NP-SLE. LN is one of the independent risk factors against remission and low disease activity.³⁰ A substantial proportion of patients with LN could not withdraw GC to achieve clinical remission. Future study with enough patients is warranted to get a robust statistical result.

It has been proposed that HCQ can reduce the risk of SLE flare and immunosuppressive agents possess steroid-sparing property.³¹ We also found a borderline decrease in flare risk associated with HCQ, but not IS usage. So in clinical practice, the majority of patients with SLE (76%–100%) maintained antimalarial treatment after GC withdrawal.^{18 19} The dose-dependent effect of IS should be considered, but unfortunately the dosage of IS was not

mentioned in any of the studies. On the other hand, the patients with IS therapy usually have more severe disease than those without IS. Additionally, recently launched belimumab has been shown to be able to reduce flare and GC daily dose in patients with LN.³² Thus, whether the application of HCQ, IS and/or biologics can prevent flare after GC discontinuation needs to be further evaluated in the future. The pharmacoeconomics and long-term safety of these drugs to replace GC for maintenance also need evaluation.

We are aware of some limitations of the study. First, although the currently available databases were retrieved, there are insufficient data on several other risk factors for lupus flare, such as the dose of GC at time of tapering and the speed of tapering, which did not allow us to perform more detailed subgroup analyses. Second, some bias may exist. Both RCT and cohort studies were included in our analysis. There were only limited studies available for some subanalysis. But this is based on the best evidence available so far with acceptable quality. Third, not all studies made enough adjustment for potential confounders. We could not fully unify the confounders either. Lastly, for the results with CI included 1, we cannot formally conclude statistical significance. Further studies with larger sample size are needed to obtain more accurate results.

In summary, this study showed an increased risk of flare among patients with SLE with SACQ after GC withdrawal. A trend of lower risk of flare was found in patients with older age and/or using HCQ, although statistical significance was not reached. Concomitant use of IS was not associated with reducing risk of flare. A new era without GC in the treatment of SLE needs introducing novel therapies and biomarkers.

Contributors ZZ was responsible for the study design, participated in its design and coordination and critically revised the manuscript. ZZ was also the guarantor. LJ and WX had full access to all the data collection, analysis, interpretation and drafted the manuscript. SF contributed to the process of data collection. All the authors listed have approved the enclosed manuscript.

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