Cardiovascular risk factors and complications in patients with systemic lupus erythematosus with and without nephritis: a systematic review and meta-analysis

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ABSTRACT

Introduction It remains unclear how the presence of renal involvement will affect the cardiovascular (CV) risk factors and complications in patients with SLE.

Methods We conducted a systematic review and meta-analysis using PubMed, EMBASE, MEDLINE and Scopus to identify studies published between 1947 and 2022 that evaluate the CV risk factors and complications in patients with SLE with and without lupus nephritis (LN).

Results 58 studies were evaluated, with 22 two-arm studies (n=8675) included in two-arm meta-analysis and 45 studies (n=385315) included in proportional meta-analysis. Patients with SLE with LN showed significantly higher risk of hypertension (HT) (OR=4.93, 95% CI=3.17 to 7.65, p<0.00001, I²=56%), hyperlipidaemia (OR=11.03, 95% CI=4.20 to 28.95, p<0.00001, I²=56%), diabetes mellitus (DM) (OR=1.88, 95% CI=1.09 to 3.25, p=0.02, I²=32%) compared with those without LN. Patients with LN showed numerically higher prevalence of myocardial infarction (OR=1.35, 95% CI=0.53 to 3.45, p=0.52, I²=79%) and cerebrovascular accident (OR=1.64, 95% CI=0.79 to 3.29, p=0.27, I²=23%) than general patients with SLE. The incidence rates of CV mortality are also increased in patients with SLE with LN compared with those without LN (11.7/1000 patient-years vs 3.6/1000 patient-years).

Conclusion Patients with SLE with LN show increased risk of CV risk factors including DM, HT and hyperlipidaemia. Early identification and optimal control of these CV risk factors may reduce the risk of CV disease and other non-CV complications.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cardiovascular disease (CVD) is an important cause of mortality in patients with SLE.
⇒ Patients with SLE were shown to have a twofold to threefold increase in the risk of CVD.

WHAT THIS STUDY ADDS

⇒ It remains unclear how the presence of lupus nephritis (LN) will impact on risk factors and complications of CVD in patients with SLE.
⇒ While several studies have reported CVD outcomes in patients with LN, they have considerable heterogeneity in the study design, patient characteristics and treatment regimens.
⇒ This meta-analysis serves to review all the current evidence and offer insight into this topic.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ With more awareness on the impact of LN on CVD outcomes, clinicians could identify and control cardiovascular risk factors at an earlier stage, reducing the chance of developing CVD and other non-cardiovascular complications.
with LN are even more complex. Conventional CV risk factors such as diabetes mellitus (DM), hypertension (HT) and dyslipidaemia were reported to be increased in patients with LN as compared with patients with SLE without nephritis.14–17 Other contributing factors for atherosclerotic CVD in patients with LN include presence of renal impairment and proteinuria.17 18 Indeed, renal insufficiency and proteinuria are both well-recognised risk factors for atherosclerotic CVD, and CVD in fact is the leading cause of mortality in patients with renal failure.19 20 While various investigators have reported the prevalence of CV risk factors in patients with LN, these studies have considerable heterogeneity in the study design, patient characteristics and treatment regimens.2 More importantly, it remains unclear how the presence of LN will impact on risk factors and complications of CVD in patients with SLE. Based on these knowledge gaps, this systematic review and meta-analysis was conducted to compare the CV risk factors and CVD in patients with SLE with or without LN.

METHODS

Search strategy and selection criteria

This meta-analysis was registered under the internal prospective register of systematic review (PROSPERO, registration ID: CRD42022314682) and conducted in accordance with the standards set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.21 We search systematically in PubMed, EMBASE, MEDLINE and SCOPUS to identify all published and prepublication studies on CVD and its risk factors in patients with SLE with and without nephritis, up to 4 March 2022 (online supplemental material 1). There is no language restriction imposed in the search.

Study selection

We included observational studies (cross-sectional study, cohort study, prospective study and retrospective study) which reported the prevalence of CVD and CVD risk factors in adult (≥18 years old) patients with SLE with and without nephritis. Studies that were used for meta-analysis of two-arm studies all involve both SLE with LN and those without LN, while studies selected for meta-analysis of proportion were general SLE cohorts (ie, included both patients with or without LN) and LN cohorts (ie, all patients had renal involvement). Case reports, editorials, reviews and animal studies were excluded. Studies were excluded if there was an overlap in subjects with another included study; hence, study subjects were only included once in any given analysis.

Data extraction and quality assessment

Data were extracted and reviewed by two independent investigators (CYW, BMYM) and disagreements were resolved by their consensus or consultation of the third reviewer.21 Published details of the study including the name of the journal, publication date, first author, study design, sample size and patient demographics (including sex, age, ethnicity) were extracted for review. Clinical data on the outcomes of interest (including prevalence of MI, CVA, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG), and prevalence of patients with dyslipidaemia, DM, HT and plaque occurrence) were retrieved. Newcastle–Ottawa Scale (NOS)22 was adopted to evaluate the quality of observational studies in meta-analysis of two-arm studies (online supplemental material 2). NOS assesses quality by three components, namely selection of study groups, comparability of cohort by design or analysis and outcomes of interest, classifying studies into having high, moderate or low risk of bias depending on the score.

Outcomes

The main outcomes of our meta-analysis were prevalence of MI, CVA, HT, hyperlipidaemia, DM and plaque occurrence in patients with SLE with and without nephritis. We also evaluated the SBP and DBP, TC, LDL, HDL and TG in the study cohorts. Definition of the outcomes given by included studies was included in online supplemental material 3.

Synthesis and analysis of data

Review Manager V.5.3 was used for meta-analysis of two-arm studies. Dichotomous outcomes were combined using OR, while continuous outcomes were combined using weighed mean difference (MD). A random-effects model was chosen to calculate the pooled MD/OR and 95% CI, assuming each study may have different estimation of underlying true effects which are distributed about an overall mean.23 Heterogeneity was analysed by I² index, which stratifies the data into minimal, moderate and substantial heterogeneity when I² value is <25%, 25–50% and >50%, respectively. Subgroup analysis was performed, stratifying the results according to age, gender, ethnicity, sample size, prevalence of DM and steroid use.

Meta-analysis of proportion was done using R, using a random-effects model due to variations among studies. Pooled estimates and their 95% CI were calculated and represented by forest plot. Heterogeneity was analysed by I² index. The pooled prevalence of outcome of interest in patients with LN and SLE was compared with z test, with z score and p value calculated. Results in prevalence were considered statistically significant if p values were <0.05.

Patient and public involvement

Patients and the public were not involved in any way.

RESULTS

Characteristics of enrolled studies

A total of 26361 studies were identified based on our search criteria in the four databases (figure 1). After removing the duplicates, 18714 studies were excluded by screening the title and abstract, leaving 186 articles for full-text review.
22 studies were included in the final meta-analysis of two-arm studies (online supplemental material 4), totalling 8675 patients with SLE, including 2295 and 6380 patients with and without LN, respectively. The studies were all conducted between 1990 and 2020, with 46% of the studies from Europe, 18% from Asia, 5% from Africa, 18% from Latin America and 14% from North America, respectively. There was a female predominance across all the studies (86.7–100%) and the age of the patients ranged from 25.7 to 49.3 years. The duration of follow-up for SLE and LN was 2–11 years and 0.5–7 years, respectively.

The meta-analysis of proportion examined 45 studies (online supplemental material 5), of which 24 studies included a total of 369,356 patients with SLE (inclusive both patients with or without LN). The remaining 21 studies provided data of patients with LN (n=15,959). The studies were conducted from 1990 to 2020.

**Association between LN and HT**

A total of 10 two-arm studies (n=5473) investigated the relationship between LN and HT (among which three also reported the mean SBP and DBP of the cohorts). Eight studies reported the OR for HT. The presence of LN was associated with higher SBP (MD=2.31, 95% CI=1.13 to 3.5, p=0.0001, I²=0%) (figure 2A) and DBP (MD=4.05, 95% CI=3.26 to 4.84, p<0.00001, I²=0%) (figure 2B), and increased risk of developing HT (OR=4.93, 95% CI=3.17 to 7.65, p<0.00001, I²=56%) (figure 2C) within the random-effects model. Subgroup analysis demonstrated that patients with SLE with LN and older than 40 years were associated with higher SBP (MD=2.20, 95% CI=0.95 to 3.45, p=0.0005,
I²=0%), DBP (MD=4.15, 95% CI=3.34 to 4.96, p<0.00001, I²=0%) and risk of HT (OR=5.22, 95% CI=4.00 to 6.82, p<0.00001, I²=0%) (online supplemental material 6), but such relationship was not observed in those younger than 40 years. Latin American patients with LN were more likely to develop HT (OR=6.07, 95% CI=1.86 to 19.85, p=0.000, I²=74%) compared with other ethnic groups (online supplemental material 6). Studies in which >50% of patients receiving corticosteroids had higher mean SBP (MD=2.20, 95% CI=0.95 to 3.45, p=0.005, I²=0%) and DBP (MD=4.15, 95% CI=3.34 to 4.96, p<0.00001, I²=0%).

Proportional meta-analysis included 17 studies (n=14442) in the LN arm \(^{10} 11 14 20 27 32 34 40 42 60 70 72-76\) and 23 studies (n=368235) of patients with SLE in general.\(^ {28-36 45-49 56 57 59-68}\) Patients with LN (online supplemental material 7A) showed significantly higher prevalence of HT than patients with SLE (online supplemental material 7B) in general (pooled prevalence: 59% (95% CI 46% to 70%) vs 27% (95% CI 20% to 35%); z=4.94, p=7.49e-07).

The impact of LN on hyperlipidaemia and DM

10 two-arm studies (n=1207) had the required data for analysing the relationship between LN and lipid profile.\(^ {4, 24} 25 35 37 38 41 43\) Seven of them included the mean total TC levels,\(^ {24} 25 35 37 38 41 43\) while six included the mean HDL, LDL and TG levels.\(^ {24} 25 35 37 41 43\) Three studies reported the OR of hyperlipidaemia.\(^ {24} 27 32\) The pooled outcomes showed that patients with SLE with LN were associated with significantly higher TC (MD=0.44, 95% CI=0.12 to 0.76, p=0.006, I²=73%) (figure 3A), LDL (MD=0.37, 95% CI=0.02 to 0.71, p=0.04, I²=70%) (figure 3B) and risk of hyperlipidaemia (OR=11.03, 95% CI=4.20 to 28.95, p<0.00001, I²=0%) (figure 3E) within the random-effects model. There was no significant association between LN and lower HDL (MD=−0.06, 95% CI=−0.11 to 0.00, p=0.06, I²=0%) or higher TG level (MD=0.13, 95% CI=−0.11 to 0.37, p=0.28, I²=64%) (figure 3D). Subgroup analysis showed that the effect of LN on lipid profile was more evident in patients younger than 40 years of age, with higher TC (MD=0.49, 95% CI=0.18 to 0.81, p=0.002, I²=70%) and LDL (MD=0.43, 95% CI=0.03 to 0.83, p=0.04, I²=71%) and lower HDL (MD=−0.06, 95% CI=−0.12 to 0.00, p=0.04, I²=0%), but such relationship was not observed in those older than 40 years. African American patients with LN were also found to have higher TC (MD=1.31, 95% CI=0.27 to 2.35, p=0.01, I²=not applicable (NA)) and LDL (MD=1.31, 95% CI=0.47 to 2.15, p=0.002, I²=NA) compared with other ethnic groups (online supplemental material 6). Proportional meta-analysis included 11 studies (n=2302)\(^ {4, 10} 14 20 27 32 34 40 42 60 70 72-76\) in LN group and 15 studies (n=326110)\(^ {28-36 45-49 52-56 59-64 66-68}\) in the SLE group. In line with the meta-analysis of two-arm studies, patients
Figure 3  The impact of lupus nephritis on (A) total cholesterol, (B) low-density lipoprotein, (C) high-density lipoprotein, (D) triglyceride, (E) hyperlipidaemia and (F) diabetes mellitus.
with LN (online supplemental material 8A) showed a significantly higher prevalence of hyperlipidaemia than patients with SLE (online supplemental material 8B) in general (pooled estimate: 42% (95% CI 24% to 62%) vs 19% (95% CI 15% to 25%); z=2.30, p=0.022).

Six two-arm studies (n=2012) reported the relationship between LN and DM.132 35 38 42 43 Our analysis revealed that patients with LN were associated with higher risk of developing DM within the random-effects model (OR=1.88, 95% CI=1.09 to 3.25, p=0.02, I²=32%) (figure 3F). The impact of LN on developing DM was significantly stronger in younger patients (OR=3.53, 95% CI=1.77 to 7.03, p=0.0003, I²=0%) and also those receiving corticosteroids (OR=1.36, 95% CI=1.13 to 1.64, p=0.0009, I²=0%) (online supplemental material 6). Proportional meta-analysis included 12 studies (n=14250) in the LN arm4 10 32 35 42 43 69 70 72 73 76 77 and 19 studies (n=282848) of patients with SLE in general36 45 47 50 52 53 55–63 65 66 68 (online supplemental material 9A), and showed numerically higher prevalence of DM than general patients with SLE, although the results did not reach statistical significance (pooled estimates: 10% (95% CI 6% to 16%) vs 5% (95% CI 3% to 10%), respectively; z=1.57, p=0.12).

**Association between LN and atherosclerotic diseases**

Six two-arm studies (n=7255) have compared the risk of atherosclerotic CVD in patients with or without LN.33 35 36 41–43 Three studies evaluated the risk of MI,33 35 42 three studies assessed the risk of CVA33 35 36 and seven studies compared the plaque occurrence in patients with SLE with or without nephritis.28–31 34 39–44 The pooled estimates revealed higher risk of developing MI (OR=1.35, 95% CI=0.53 to 3.45, p=0.52, I²=78%) (figure 4A) and CVA (OR=1.64, 95% CI=0.79 to 3.39, p=0.27, I²=23%) (figure 4B) in patients with SLE with LN, but the results did not reach statistical significance. Subgroup analysis did not show any significant trends (online supplemental material 6). The presence of LN also did not show any significant relationship with plaque occurrence (OR=0.85, 95% CI=0.59 to 1.22, p=0.37, I²=73%) (figure 4C).

Proportional meta-analysis of MI prevalence included five studies (n=13276) in the LN arm,35 42 70 72 73 and eight studies (n=42259) of patients with SLE in general.45 48–50 54–63 Patients with LN showed numerically higher prevalence of MI, although the difference did not reach statistical significance (pooled estimates: 8% (95% CI 4% to 14%) vs 4% (95% CI 2% to 10%), respectively; z=1.06, p=0.29) (online supplemental material 10A,B). CV mortality was reported only in one study, in which patients with LN showed higher incidence of CV mortality than those without LN (11.7/1000 patient-years vs 3.6/1000 patient-years).33

As for proportional meta-analysis of the prevalence of CVA, five studies (n=12830)35 36 71–73 with exclusively patients with LN and eight studies (n=52631)45 48–50 53–55 62 with general patients with SLE were included. The LN group (online supplemental material 11A) showed numerically higher prevalence of CVA than general patients

Figure 4 The impact of lupus nephritis on (A) myocardial infarction, (B) cerebrovascular accident and (C) plaque occurrence.
with SLE (online supplemental material 11B), but the difference did not reach statistical significance (pooled estimates: 10% (95% CI 5% to 17%) vs 8% (95% CI 6% to 11%), respectively; z=0.56, p=0.57).

**DISCUSSION**

The short-term and long-term survival of patients with SLE and LN have improved remarkably over the past few decades, owing to the advances in immunosuppressive and general medical treatments.78–81 With better early survival, CV morbidity and mortality have become a growing concern in the long-term management of patients with SLE and LN.1,82 Our meta-analysis results showed that the presence of LN in patients with SLE was associated with increased risk of various conventional CV risk factors including HT, dyslipidaemia and DM, and also elevated odds of CV mortality. Our observations are clinically important because these CV risk factors are potentially amenable to treatment and their adequate control can modulate the risk of CV morbidity and mortality.

In this meta-analysis, patients with SLE with LN showed a fivefold risk of developing HT compared with those without nephritis. The prevalence rates of HT were up to 80% among patients with SLE with LN, and the SBP and DBP were both significantly higher than patients with renal involvement. The kidneys are an important organ for blood pressure regulation, and hence HT is highly prevalent among patients with CKD and often an early indication of renal impairment.83–85 The increased propensity for HT in patients with LN can be explained by cumulative renal damage caused by previous severe nephritis or repeated renal flares. The high rates of HT in patients with LN call for more aggressive blood pressure control to reduce proteinuria and retard further deterioration of renal function. Our findings also suggested that patients with LN older than 40 years are particularly affected as age per se is an important risk factor for HT. Our subgroup analysis revealed that Latin American patients with LN had significantly higher risk of HT compared with other ethnicities. Indeed, Latin Americans are recognised to have more resistant HT compared with patients of other racial backgrounds.86–87

Our results showed that patients with SLE with LN were associated with significantly higher TG, LDL and risk of hyperlipidaemia compared with those without LN. One previous study from our group also reported high prevalence of dyslipidaemia (up to 60%) in patients with LN despite achieving disease quiescence.14 Dyslipidaemia in patients with LN can be contributed by concomitant immunosuppressive medications (eg, low-dose corticosteroids), low-grade proteinuria, chronic renal insufficiency and systemic inflammatory states.88–90 Our subgroup analysis further showed that patients with LN younger than 40 years appeared to be more affected. In general, younger patients tend to have lower risk of dyslipidaemia, and the presence of renal abnormalities such as proteinuria and renal impairment in patients with LN may predispose them to aberrant lipid profiles. While previous studies suggested that African Americans generally show more favourable lipid profiles compared with other ethnicities,88–92–94 our subgroup analysis indicated that the presence of LN may nullify such racial advantage.

Our present meta-analysis data revealed that patients with SLE with LN conferred almost a twofold risk of DM compared with those without LN. The increased propensity for DM is highly related to the use of corticosteroids for induction-maintenance treatment for LN, and indeed our subgroup analysis corroborated with this notion. While young individuals generally have low risk of DM, our data suggested that the presence of LN significantly elevates the odds of DM in young patients with SLE. The development of DM is clinically important because this not only increases the risk of macrovascular complications such as MI or CVA, but also the various microvascular complications including diabetic nephropathy, retinopathy and neuropathy.95–97 It remains unknown whether the growing use of calcineurin inhibitors (eg, tacrolimus or voclosporin) for the management of LN may further increase the risk of DM in patients with SLE.98,99 The elevated risk of DM and HT in patients with LN receiving corticosteroids calls for better attempts and strategies to minimise overall steroid exposure, especially in patients with stable disease.100

With increase in various conventional CV risk factors, one would expect a significantly higher risk and prevalence of CVD in patients with SLE with LN compared with those without LN. In this meta-analysis, the presence of LN in patients with SLE was associated with numerically higher prevalence and odds of MI and CVA compared with those without LN, though the results did not reach statistical significance. This may be related to the limited number of studies that have included both patients with SLE with LN and those without LN. While it appeared that the results were ‘numerically higher’ in the LN group, it could equally suggest that there was indeed no significant difference even if the sample size was increased. It also remains possible that SLE per se is a very strong risk factor for CVD, and that the impact of LN cannot be fully demonstrated. Of note, our proportional meta-analysis showed that the prevalence of MI was doubled in patients with LN compared with patients with SLE in general. Furthermore, our data also suggest that patients with SLE with LN have substantially higher CV mortality compared with those without LN. Indeed, CVD is a leading cause of death in patients with SLE, conferring a 13-fold risk of mortality compared with age-matched and gender-matched general population.3 Apart from having more traditional CV risk factors, the increased risk of CVD and CV mortality in patients with LN may be explained by endothelial dysfunction and increased prothrombotic tendency, as evidenced by elevated levels of endothelial cell function markers such as platelet endothelial cell adhesion molecules,101 vascular endothelial-cadherin, serum anti-endothelial

There are a few key limitations to this meta-analysis. First, there are few studies with CVD data on both patients with LN and those without LN, making the assessment of the impact of LN on CVD in patients with SLE difficult. During the screening process, we found that many important and well-conducted studies (some with very large patient numbers) were excluded because they did not have clinical data for both arms. To address this problem, we conducted the proportional meta-analysis to supplement the results of two-arm meta-analysis, which calculates the weighted average of each arm separately and comparing them with statistical method. We have chosen to compare general patients with SLE with patients with LN, as there were not any studies that solely reported on patients with SLE without nephritis. The potential drawback was that the data in the SLE arm would be contaminated by patients with LN inside the SLE cohort. In addition, proportional meta-analysis is bound to have between-study bias as the baseline characteristics of the LN group and SLE group were not proven to be comparable. To circumvent these issues, we have interpreted the results of proportional meta-analysis with respect to the findings in two-arm meta-analysis, and the data/conclusions were largely concordant. Furthermore, definitions of outcomes are often incomplete in the included studies, especially those in proportional meta-analysis. Other issues include that some studies may have defined HT by the use of anti-HT drugs, and yet patients with LN often receive ACE inhibitors/angiotensin receptor blockers for proteinuria reduction rather than treatment for HT. In addition, data on other major adverse cardiovascular events outcomes such as heart failure are also lacking. There is insufficient information to analyze the effect of immunosuppressive treatments and anti-malarials on CV risk factors and CVD in patients with LN. With growing use of biologics and new calcineurin inhibitors, future studies are worthwhile to evaluate how these novel therapeutics will attenuate the CV risk factors and CVD in patients with LN.

Lastly, study of hard CVD events and mortality is prone to survivorship bias, as only survivors could be studied, while data of non-survivors are overlooked. Results are also potentially confounded by age—an important risk factor for CVD and mortality, as patients in the LN group were generally younger than the non-LN group (online supplemental material 4).

CONCLUSION

Patients with SLE with LN show increased risk of CV risk factors including DM, HT and hyperlipidaemia. Early identification and optimal control of these CV risk factors may reduce the risk of CVD and other non-CV complications.

Contributors CYW and BMYM contributed to data collection. CYW, DZ and WC performed statistical analysis. DHYH and TMC conceived the study and were in charge of overall direction and planning. All authors discussed and commented on the manuscript.

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