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Evaluating Sex Differences in the Characteristics and Outcomes of Lupus Nephritis: A Systematic Review and Meta-Analysis

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Keywords
Lupus nephritis · Male · Men · Gender · Sex · Meta-analysis

Abstract
Introduction: More frequent and severe lupus nephritis (LN) has been reported in men compared to women, but data are limited and inconsistent. We conducted a meta-analysis of the literature to compare the histopathologic findings and outcomes between men and women with biopsy-proven LN. ***Methods:*** A systematic search of MEDLINE, Embase, Cochrane, and Web of Science databases was conducted through February 2021. Clinical information was extracted and synthesized from 25 studies that met inclusion criteria (1,210 men and 6,635 women). Pooled odds ratios (OR) with corresponding 95% confidence intervals (CIs) were generated via meta-analysis, and meta-regression was performed to assess the impact of several covariates, both using random-effects models. ***Results:*** Twenty studies reported kidney histopathology, eleven reported kidney outcomes, and eight reported mortality rates. Men had greater odds of class IV ± V LN (OR 1.26, 95% CI: 1.01–1.56), and the composite of end-stage kidney disease, persistent eGFR <15 mL/min or doubling of serum creatinine (OR 2.20, 95% CI: 1.59–3.06), and lower odds of complete remission (OR 0.52, 95% CI: 0.39–0.68). Mortality was not statistically significantly different between sexes (OR 1.50, 95% CI: 0.92–2.46). Meta-regression did not reveal statistically significant study-level relationships between sex differences in any of the covariates that could account for the greater odds of worse kidney outcome in males. ***Conclusion:*** Our analysis confirms the association between male sex and increased severity of LN as well as worse kidney outcomes. Larger prospective studies are needed to validate this association and inform treatment strategies adapted to this population.

Introduction

Systemic lupus erythematosus (SLE) is an idiopathic connective tissue disorder that incites a wide array of clinical and immunologic features [1]. An estimated 1.5 million people suffer from SLE in the USA, up to 22% of whom are men [2]. Lupus nephritis (LN) affects up to 60% of all patients with SLE, about 10% of whom progress to end-stage kidney disease (ESKD) [3]. Per the US Renal Data System database from 1995 to 2010, 18% of patients with ESKD due to LN were male [4].

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The underlying reason for a female preponderance is incompletely understood, but likely relates to the interactions between endogenous sex hormones and the immune system [5]. Debate exists whether a distinct type of SLE affects men, as more severe disease with more frequent involvement of specific organ systems, in particular LN, has been reported [6, 7]. However, these findings have been inconsistent, with the available data derived predominantly from retrospective studies with small numbers of participants [2, 8]. Furthermore, kidney involvement is frequently reported based on clinical parameters alone without correlation with biopsy data, even in larger, more recent cohorts [9–11]. This is problematic, as conventional markers of disease activity such as proteinuria and measures of kidney function obtained at the time of diagnosis do not adequately predict long-term outcomes [12, 13], and may not correlate with histological disease activity in a substantial number of patients [14, 15]. A large study of 2,188 men with SLE from the US Veterans Administration Healthcare System reported no difference in the prevalence of kidney disease among the sexes, and it remains controversial whether sex independently contributes toward kidney involvement and outcomes in patients with LN [16].

Given these inconsistencies, we performed a systematic review of the available data to assess whether there are differences in LN histopathology and outcomes between men and women. We further aimed to evaluate if differences in outcomes could be explained on the basis of differences in clinical characteristics, histopathologic findings, or treatments used.

Methods

Search Strategy

The "Meta-analysis of observational studies (MOOSE)" guidelines for systematic reviews were used to plan the study and we adhered to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines [17, 18]. A comprehensive literature search from inception through February 3, 2021, was conducted using the MEDLINE (PubMed, NCBI), Embase (Embase.com, Elsevier), Cochrane Central Register of Controlled Trials (Cochrane Library, Wiley), and Web of Science Core Collection databases. No language restriction was applied. An experienced librarian (W.L.S.) assisted with the search methodology. The core concepts of "lupus nephritis" and "sex/gender" and their corresponding subject heading terms were searched in the above databases. The search strategies for each database are provided in online supplementary Tables 1–4 (for all online suppl. material, see https://doi.org/10.1159/000535981). We added manual searching and cross-referencing to the computerized literature search. Results were exported to EndNote 19 (Clarivate, Philadelphia, PA, USA), and duplicates were removed by successive algorithmic deduplication and manual inspection.

Inclusion and Exclusion Criteria

We limited screening to controlled trials and observational studies that included adult patients with biopsy-proven LN and excluded studies with only pediatric patients. Abstracts, case reports, case series (<10 male patients), editorials, guidelines, and review articles were excluded.

Screening and Data Extraction

Two independent investigators (S.B.M. and D.M.) conducted the screening and data extraction. Conflict resolution was achieved through discussion. Neither reviewer was blind to journal titles, study authors, or institutions. Initially, titles and abstracts were screened followed by evaluation of full texts. Data including demographic and clinical variables and individual study outcomes were recorded. Clinical variables extracted included age, sex, serum creatinine (Cr), proteinuria, serum albumin, presence of hypertension, presence of nephrotic syndrome, presence of hypocomplementemia (low C3 and/or C4), positivity for antinuclear antibody, positivity for anti-double-stranded DNA, treatments used for immunosuppression induction, and the proportions of participants that achieved remission.

We aimed to evaluate and compare the following:

- Kidney biopsy findings to compare the frequency of proliferative (class III or IV ± V) and diffuse proliferative (class IV ± V) versus membranous only (class V) LN, and activity and chronicity index scores between men and women.
- The odds of patient survival and key kidney outcomes for men compared to women. Kidney outcomes were pooled and assessed as a composite, for which we used the authors' own definition that included ESKD requiring chronic dialysis or kidney transplantation, estimated GFR persistently <15 mL/min or persistent doubling of serum Cr.

Data Synthesis and Statistical Analysis

Statistical analysis was performed with Open Meta-Analyst (CEBM, University of Oxford, Oxford, UK). An online tool by Hozo et al. [19] was used to convert median and range to mean and standard deviation for the tables. Given the presumed heterogeneity in the included studies, the DerSimonian-Laird approach using a random-effects model was used a priori [20]. For binary outcomes, odds ratios (OR) for men compared to women with 95% confidence intervals (CI) and p values were generated. Continuous outcomes were compared using the mean difference (MD) for men relative to women with 95% CI and p values generated. A p value of <0.05 was considered statistically significant for each outcome. Study heterogeneity was assessed using the Cochran's Q and I^2 statistics [21], with values >30% for the I^2 accompanied by a p value of <0.10 for the Q statistic considered substantial heterogeneity. To assess the influence of individual studies on the pooled estimate (i.e., sensitivity analysis), estimates were recomputed using the leave-one-out method. To assess for potential bias introduced by studies including only a small number of participants, estimates were recomputed using only the studies that had included greater than 25 men. Random-effects meta-regression analyses were performed to assess the influence of sex differences in each covariate on the association between sex and the

composite kidney outcome. Regression coefficients (β_1) with 95% CI and p values (<0.05 considered statistically significant) were generated. The meta-regression analyses were carried out using the *metafor* package (W. Viechtbauer, 2010) running in R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

Bias Assessment

Risk of bias assessment was performed using the Newcastle-Ottawa Scale (NOS) [22] for studies that reported kidney and mortality outcomes. This was performed independently by two authors (S.B.M. and M.A.), with disagreements resolved by mutual discussion. For comparability of cohorts, a point was given if the study controlled for immunosuppressive treatments, and an additional point was assigned if the study controlled for one more important factor (including age, histological class of LN, baseline clinical parameters such as baseline Cr or proteinuria). A high risk of bias was assigned if a study failed to control for immunosuppressive treatments. We considered a follow-up of at least 1 year to be adequate. An overall risk of bias rating was then assigned for each study: a high risk was assigned if the study received a high risk of bias rating in any domain, an intermediate risk was assigned if there was an intermediate risk of bias in any domain, and a low risk of bias rating was reserved for studies that received a low risk rating in all domains. Publication bias was assessed using funnel plots (qualitative) and Egger's regression analysis (quantitative with a p value <0.05 considered significant). Results are provided as supplementary data.

Results

Study Selection and Characteristics

The search strategy yielded a total of 555 articles (Fig. 1). 403 studies were screened by title and abstract after removal of duplicates and 345 articles were excluded. Another 33 articles were excluded after full-text screening. Twenty-five studies were included in the final analyses, with a total of 7,845 patients with biopsy-proven LN (1,210 men and 6,635 women) [6, 23–46].

The included articles were published between 1993 and 2021 and included cohorts from diverse parts of the world (Table 1). The WHO [47] or ISN/RPS [48] classifications of LN were utilized in all but one study that used descriptive criteria to report histopathology [45]. For this study, focal proliferative and diffuse proliferative disease was considered equivalent to class III ± V and class IV ± V LN, respectively, and membranous disease equivalent to class V LN.

The outcomes reported in each study are summarized in Table 1. Table 2 summarizes the number of studies with the corresponding numbers of male and female participants for each variable, as well as the associated pooled estimates (OR or MD).

LN Histopathology

Twenty-two studies compared kidney biopsy findings between men and women [6, 23–27, 29, 30, 32–45]. Based on pooled estimates, men had a statistically significant greater likelihood than women of having diffuse proliferative (class IV ± V) LN (OR 1.26, 95% CI 1.01–1.56) (Fig. 2) and numerically greater odds of proliferative (class III or IV ± V) LN (OR 1.05, 95% CI: 0.83–1.33) (online suppl. Fig. 1). There was substantial heterogeneity in both results (I^2 = 35.67%, p = 0.06, and I^2 = 41.86%, p = 0.02, respectively). Using the leave-one-out method, results were consistent with OR ranging from 1.20 to 1.32 for class IV ± V LN (online suppl. Fig. 2). When analysis was restricted to studies that recruited >25 men, the pooled ORs for class IV ± V and class III or IV ± V disease were 1.40 (95% CI: 1.17–1.67) and 1.18 (95% CI: 0.98–1.43), respectively, with minimal heterogeneity in both results (I^2 = 0%, p = 0.77 and I^2 = 0%, p = 0.62, respectively) (online suppl. Figs. 3, 4). Given the disappearance of between-study heterogeneity when smaller studies were excluded, these findings may reflect selective reporting bias.

Analysis stratified by region is provided in online supplementary Figures 5 and 6. The largest number of included studies was from Asia, with statistically significant higher pooled ORs for both class IV ± V (OR 1.48, 95% CI: 1.19–1.83, I^2 = 0%, p = 0.65) and class III or IV ± V LN (OR 1.34, 95% CI: 1.04–1.72, I^2 = 0%, p = 0.66) in this region. Results for other regions were not statistically significant.

The pooled OR for membranous (class V only) LN showed no significant difference (OR 0.89, 95% CI: 0.69–1.15, I^2 = 19.64%, p = 0.21) (online suppl. Fig. 7). Results were consistent in the leave-one-out analysis (OR range 0.85–0.94) and when restricting the analysis to studies that recruited >25 men (OR 0.80, 95% CI: 0.60–1.08, I^2 = 27.0%, p = 0.19) (online suppl. Figs. 8, 9, respectively). Results remained nonsignificant with analysis stratified by region (online suppl. Fig. 10).

Activity and chronicity indices were reported in seven studies [24, 28, 29, 36, 38, 39, 44]. Men had numerically greater activity (MD 1.11, 95% CI: −0.07–2.29, I^2 = 96.69%, p < 0.001) and chronicity index scores (MD 0.42, 95% CI: −0.04–0.89, I^2 = 93.81%, p < 0.001) by small margins with substantial heterogeneity in both results (online suppl. Figs. 11, 12, respectively).

Clinical Variables

Thirteen studies compared age at diagnosis of LN [24, 27–29, 33, 36, 37, 39, 40, 42–44, 46] that ranged from a mean of 23.2–38.8 years for men and 24.7–35.2 years for women. The pooled MD between the sexes for age was

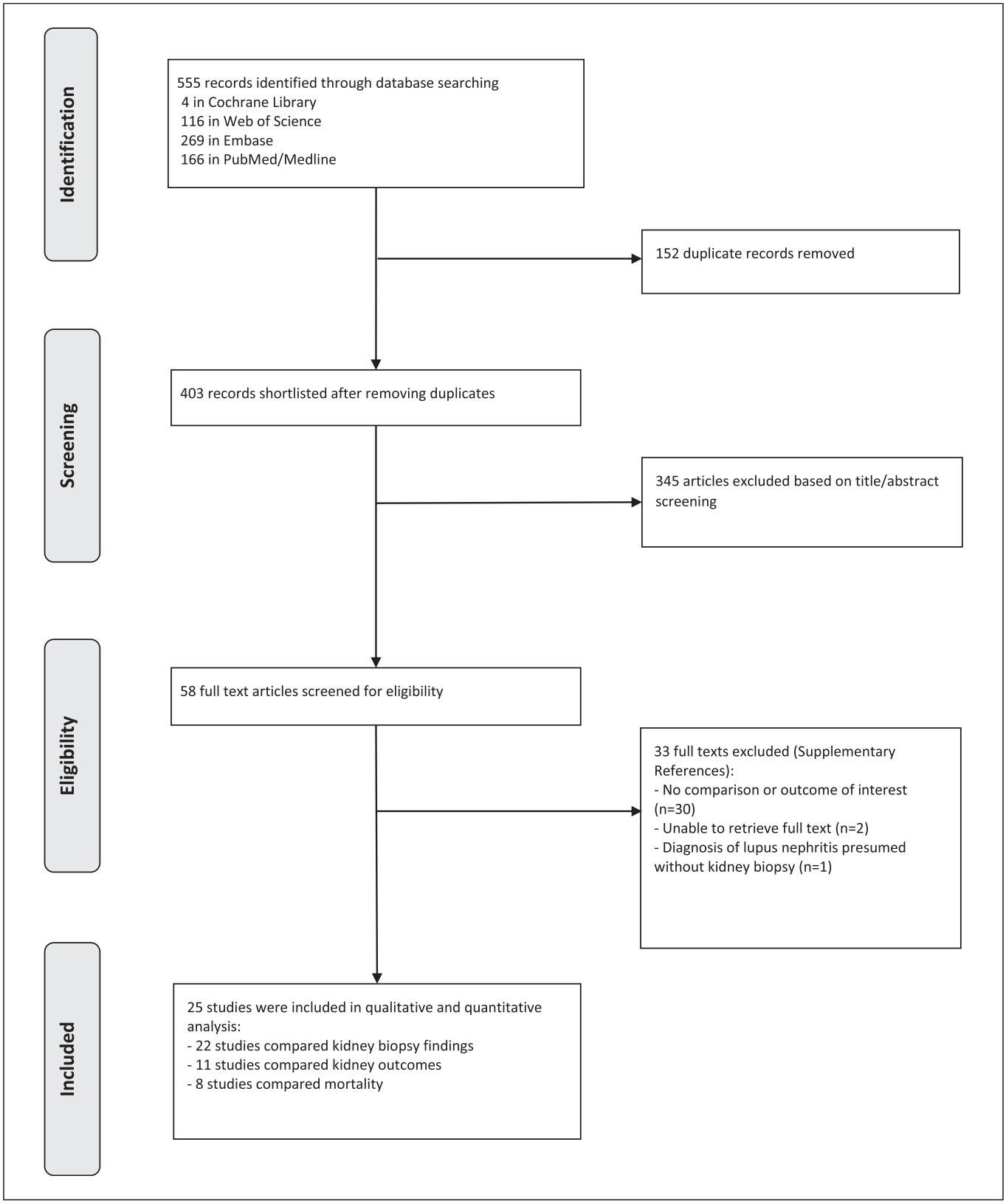

Fig. 1. PRISMA flow diagram.

Table 1. Characteristics of included studies

Study	Year	Country	No. of patients		Outcomes				
					kidney outcome			mortality	
			male	female	definition used	male, %	female, %	male, %	female, %
Bhinder et al. [23]	2010	USA	15	77	–	–	–	–	–
De Carvalho et al. [24]	2010	Brazil	11	70	ESKD[c]	36	20	18	7
De Oliveira et al. [25]	2020	Brazil	37	198	–	–	–	–	–
Faezi et al. [26]	2014	Iran	111	791	–	–	–	–	–
Farah et al. [27]	2019	Jordan	11	68	ESKD	45	22	No difference between the sexes (raw data not provided)[e]	
Hsu et al. [28]	2011	Taiwan	17	104	Doubling of Cr[d]	57*	17	-	-
Khajehdehi et al. [29]	1997	Iran	17	100	ESKD	53*	19	29*	9
Koh et al. [30]	1994	Singapore	21	18	–	–	–	–	–
Kono et al. [31]	2014	Japan	36	150	ESKD	11*	3	8	7
Liu et al. [32]	2017	China	42	306	–	–	–	12	7
Molina et al. [6]	1996	Colombia and Mexico	37	314	–	–	–	–	–
Ongajyooth et al. [33]	1994	Thailand	45	269	–	–	–	11	16.5
Pande et al. [34]	1994	India	15	89	–	–	–	–	–
Patwardhan et al. [35]	2012	India	14	116	–	–	–	–	–
Peng et al. [36][a]	2018	China	68	379	Doubling of serum Cr or eGFR <15 mL/min or ESKD	18	11	No difference between the sexes (raw data not provided)[e]	
Ramírez-Sepúlveda et al. [37]	2019	Sweden	66	199	eGFR <15 mL/min	30*	12	27	26
Shaharir et al. [38]	2019	Malaysia	33	184	–	–	–	–	–
Singpan et al. [39]	2021	Thailand	94	344	ESKD	4.5	8	–	–
Soni et al. [40]	2008	India	35	200	–	–	–	–	–
Soto et al. [41]	2004	Mexico	16	59	–	–	–	–	–
Tang et al. [42][a]	2015	China	102	579	–	–	–	–	–
Urrestarazú et al. [43]	2017	Uruguay and Spain	50	50	ESKD	26	30	6.5	6
Wang et al. [44]	2012	China	45	270	Doubling of serum Cr or ESKD	20*	11.5	4*	1
Wen et al. [45][b]	1993	China	19	140	–	–	–	–	–
Yang et al. [46]	2015	China	253	1,561	eGFR <15 mL/min	60*	27	–	–

[a]Both studies included patients from the same center in West China over time points with some overlap: the study by Tang et al. recruited patients from June 2006 to June 2012, while Peng et al. recruited patients from June 2010 to June 2016. [b]Lupus nephritis was categorized as minimal change, mesangioproliferative, focal proliferative, diffuse proliferative, and membranous disease in this study. [c]ESKD: defined as permanent dialysis or kidney transplantation in all studies except Khajehdehi et al. who used small size kidneys with Cr >5 mg/dL as their criteria. [d]Serum creatinine. [e]Unable to include results in the pooled analysis as patient-level data not provided. *Difference between men and women statistically significant with a p value of <0.05.

Table 2. Clinical variables and outcomes of interest with corresponding numbers of participants and pooled estimates

Variable	Number of studies reporting	Male, *N* (range of reported means)	Female, *N* (range of reported means)	Pooled estimate OR[e] (95% CI) or MD[f] (95% CI)	Heterogeneity metrics
LN histology					
Proliferative LN[a] (class III or IV±V), %	21	893	4,752	OR 1.05 (95% CI: 0.83, 1.33)	I^2 = 41.86% Het. p[g] = 0.02
Diffuse proliferative LN (class IV±V), %	20	788	4,571	**OR 1.26 (95% CI: 1.01, 1.56)**	I^2 = 35.67% Het. p = 0.06
Membranous LN (class V only), %	20	821	4,586	OR 0.89 (95% CI: 0.69, 1.15)	I^2 = 19.64% Het. p = 0.21
Activity index	7	285 (4–10.1)	1,451 (3–10)	MD 1.11 (95% CI: −0.07, 2.29)	I^2 = 96.69% Het. p < 0.001
Chronicity index	7	285 (1.5–4.5)	1,451 (1.3–4)	MD 0.42 (95% CI: −0.04, 0.89)	I^2 = 93.81% Het. p < 0.001
Clinical					
Age, years	13	856 (23.2–38.8)	4,639 (24.7–35.2)	MD 0.18 (95% CI: −1.62, 1.97)	I^2 = 75.19% Het. p < 0.001
LN disease duration, months	6	330 (2.8–45.6)	2,113 (2.6–57.6)	MD −2.35 (95% CI: −7.68, 2.98)	I^2 = 85.92% Het. p < 0.001
Serum creatinine, mg/dL	10	762 (1.3–3.2)	4,272 (0.9–2)	**MD 0.39 (95% CI: 0.24, 0.55)**	I^2 = 67.36% Het. p = 0.001
Proteinuria, g/day or UPCR[b]	10	762 (3.2–6.9)	4,272 (2.9–6.3)	**MD 0.72 (95% CI: 0.06, 1.37)**	I^2 = 84.18% Het. p < 0.001
Serum albumin, g/dL	5	285 (2–2.6)	1,847 (2.2–2.8)	**MD −0.23 (95% CI: −0.32, −0.13)**	I^2 = 53.37% Het. p = 0.07
Nephrotic syndrome, %	5	312	1,808	OR 1.12 (95% CI: 0.74, 1.69)	I^2 = 48.66% Het. p = 0.10
Hypertension, %	5	302	1,738	OR 1.22 (95% CI: 0.76, 1.97)	I^2 = 62.19% Het. p = 0.03
Serology					
Low complement (C3 or C4), %	5	325	1,672	**OR 1.68 (95% CI: 1.26, 2.24)**	I^2 = 0% Het. p = 0.443
ANA[c] positivity, %	5	323	1,827	OR 0.83 (95% CI: 0.44, 1.57)	I^2 = 21.12% Het. p = 0.28
Anti-ds-DNA[d] positivity, %	8	445	2,571	OR 1.06 (95% CI: 0.80, 1.39)	I^2 = 23.02% Het. p = 0.25
Treatment					
Cyclophosphamide, %	5	197	903	OR 1.41 (95% CI: 0.68, 2.90)	I^2 = 70.01% Het. p = 0.01
Mycophenolate mofetil, %	3	163	699	OR 0.90 (95% CI: 0.53, 1.53)	I^2 = 0% Het. p = 0.38
Outcomes					
Complete remission, %	5	298	1,542	**OR 0.52 (95% CI: 0.39, 0.68)**	I^2 = 0% Het. p = 0.56

Table 2 (continued)

Variable	Number of studies reporting	Male, *N* (range of reported means)	Female, *N* (range of reported means)	Pooled estimate OR[e] (95% CI) or MD[f] (95% CI)	Heterogeneity metrics
Complete or partial remission, %	5	298	1,542	OR 0.54 (95% CI: 0.25, 1.19)	I^2 = 85.29% Het. $p < 0.001$
Composite kidney outcome, %	11	611	3,179	**OR 2.20 (95% CI: 1.59, 3.06)**	I^2 = 31.15% Het. $p = 0.15$
Mortality, %	8	319	1,829	OR 1.50 (95% CI: 0.92, 2.46)	I^2 = 30.04% Het. $p = 0.19$

Statistically significant estimates are in bold. [a]Lupus nephritis. [b]Urine protein-to-creatinine ratio. [c]Antinuclear antibody. [d]Anti-double-stranded DNA. [e]OR for men relative to women. [f]MD for men relative to women. [g]Heterogeneity *p* value.

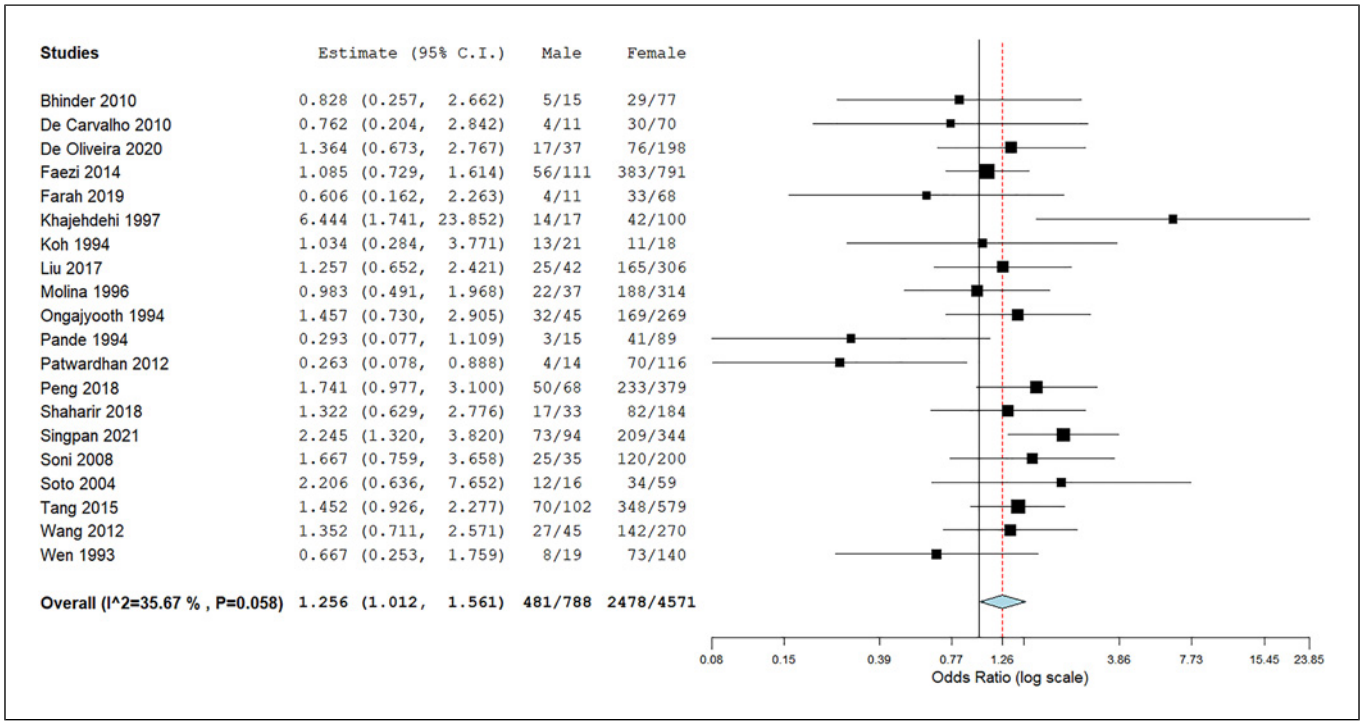

Fig. 2. Forest plot showing the estimated OR with their 95% CIs for diffuse proliferative (class IV ± V) lupus nephritis for men compared to women. CI, confidence interval.

0.18 (95% CI: −1.62–1.97, I^2 = 75.19%, $p < 0.001$) (online suppl. Fig. 13). Six studies reported the duration of LN before biopsy [24, 29, 33, 36, 42, 44]. This ranged from a mean of 2.8–45.6 months for men and 2.6–57.6 months for women with a pooled MD of −2.35 (95% CI: −7.68–2.98, I^2 = 85.92%, $p < 0.001$) (online suppl. Fig. 14).

Cr and proteinuria were reported in ten studies [24, 28, 33, 36, 39, 40, 42–44, 46]. Cr ranged from a mean of 1.3–3.2 mg/dL for men and 0.9–2 mg/dL for women, while proteinuria ranged from a mean of 3.2–6.9 g/day for men and 2.9–6.3 g/day for women. Men had statistically significant higher levels of both Cr (MD 0.39, 95% CI: 0.24–0.55, I^2 = 67.36%, $p = 0.001$) and proteinuria (MD 0.72, 95% CI: 0.06–1.37, I^2 = 84.18%, $p < 0.001$) with both results exhibiting substantial heterogeneity (online suppl. Figs. 15, 16, respectively). Five studies compared serum albumin levels [24, 28, 33, 36, 42] that ranged from a mean of 2–2.6 g/dL for men and 2.2–2.8 g/dL for women.

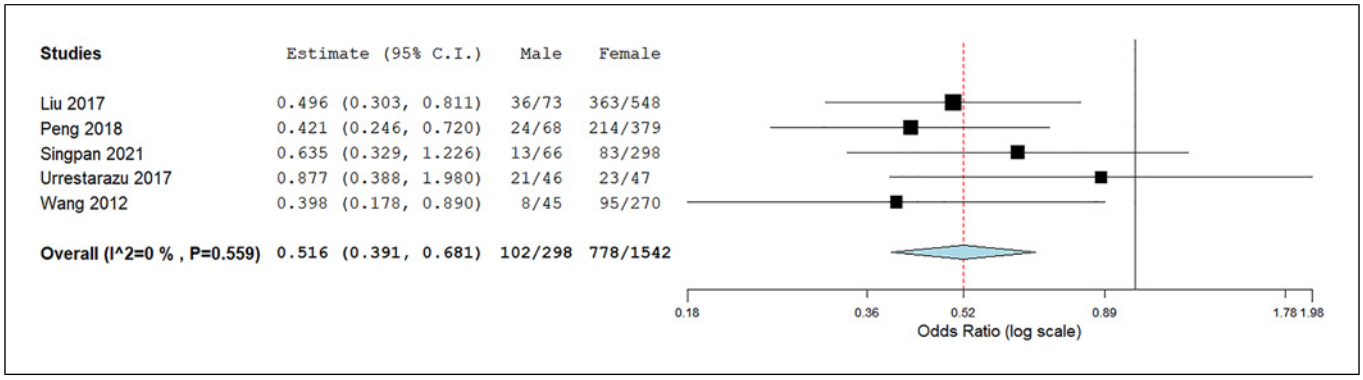

Fig. 3. Forest plot showing the estimated OR with their 95% CIs for complete remission for men compared to women. CI, confidence interval.

Men had statistically significant lower levels of serum albumin (MD −0.23, 95% CI: −0.32 to −0.13, I^2 = 53.37%, p = 0.07) (online suppl. Fig. 17). There was no significant difference between the sexes in the frequency of nephrotic syndrome and hypertension (online suppl. Figs. 18, 19, respectively).

Regarding serologies, five studies compared the proportion of participants with low complement levels between the sexes [24, 29, 36, 39, 42]. Men were statistically significantly more likely to have hypocomplementemia (OR 1.68, 95% CI: 1.26–2.24, I^2 = 0%, p = 0.443) (online suppl. Fig. 20). There was no significant difference in the pooled estimates for antinuclear antibody or anti-double-stranded DNA positivity between the sexes (online suppl. Figs. 21, 22, respectively).

Treatment and Outcomes

Treatment

Five studies reported immunosuppressive treatments [28, 29, 36, 43, 44]. Cyclophosphamide was used in all five cohorts, with no difference in the frequency of use between men and women but with substantial heterogeneity between studies (OR 1.41, 95% CI: 0.68–2.90, I^2 = 70.01%, p = 0.01) (online suppl. Fig. 23). The study by Khajehdehi et al. [29] was the only study with a significantly higher proportion of men treated with cyclophosphamide and accounted for most of the heterogeneity (I^2 decreased to 0% when this study was excluded).

Three studies reported the frequency of use of mycophenolate mofetil [36, 43, 44], for which the pooled estimate revealed no difference between men and women (OR 0.90, 95% CI: 0.53–1.53, I^2 = 0%, p = 0.38) (online suppl. Fig. 24). Cyclophosphamide use was also reported in all three studies, and the frequency of its use was similar between the sexes in each cohort.

Other immunosuppressive agents used in the included cohorts were azathioprine [28, 43, 44], calcineurin inhibitors [28, 36], and leflunomide [44]. There were no statistically significant differences in the use of any of these agents between the sexes.

Remission

Five studies compared rates of remission between sexes [32, 36, 39, 43, 44]. Mean follow-up ranged from 1.1 to 10 years. The definitions of complete (CR) and partial remission varied across studies and are listed in online supplementary Table 5, but were generally similar with CR comprising return of Cr to normal or prior baseline and decrease in proteinuria to <0.5 g/day. Men had statistically significant lower odds of CR (OR 0.52, 95% CI: 0.39–0.68, I^2 = 0%, p = 0.56) (Fig. 3). The odds of any remission (complete or partial) were not significantly different between the two sexes although there was substantial heterogeneity between studies (OR 0.54, 95% CI: 0.25–1.19, I^2 = 85.29%, p < 0.001) (online suppl. Fig. 25).

Composite Kidney Outcome and Mortality

Eleven studies compared kidney outcomes [24, 27–29, 31, 36, 37, 39, 43, 44, 46]. Mean follow-up ranged from 1.4 to 12.2 years. Men had statistically significant higher odds of developing the composite kidney outcome (OR 2.20, 95% CI: 1.59–3.06, I^2 = 31.15%, p = 0.15) (Fig. 4). This finding was consistent in the leave-one-out analysis (OR range 2.08–2.42) (online suppl. Fig. 26). Eight studies compared mortality between the sexes [24, 29, 31–33, 37, 43, 44], for which the pooled OR did not reveal a statistically significant difference (1.50, 95% CI: 0.92–2.46, I^2 = 30.04%, p = 0.19) (Fig. 5).

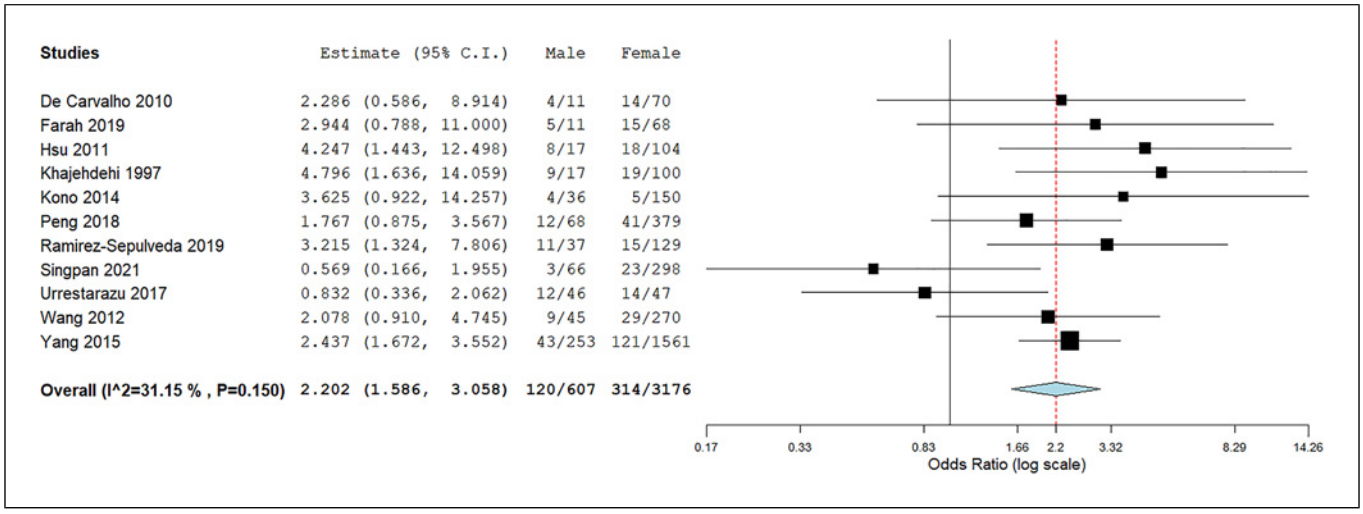

Fig. 4. Forest plot showing the estimated OR with their 95% CIs for the composite kidney outcome for men compared to women. CI, confidence interval.

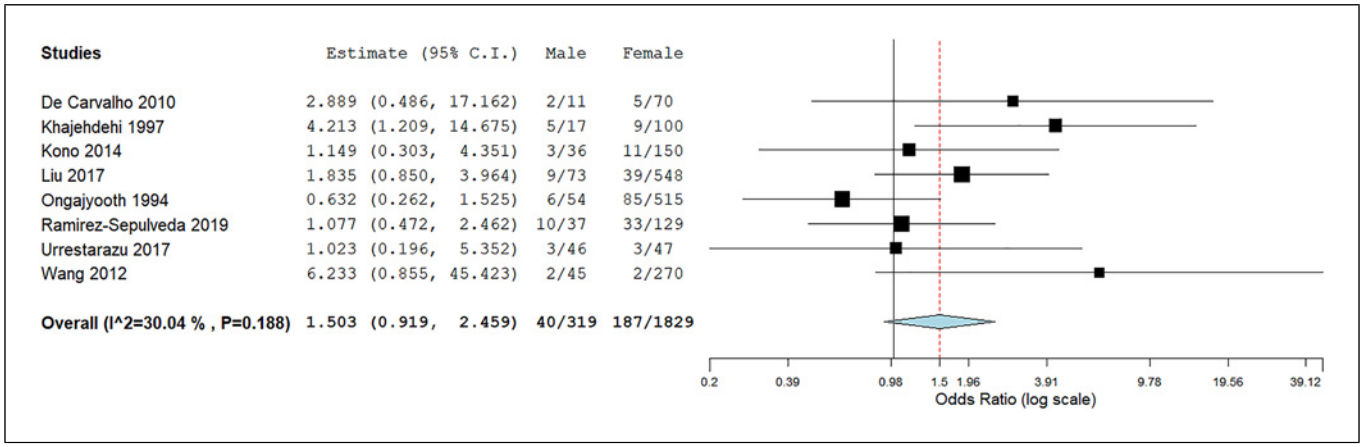

Fig. 5. Forest plot showing the estimated OR with their 95% CIs for mortality for men compared to women. CI, confidence interval.

Meta-Regression

We conducted a meta-regression analysis to explore whether the significantly greater OR of worse composite kidney outcome in men was attributable to sex differences in demographic or clinical characteristics. We analyzed age, Cr, proteinuria, activity and chronicity indices, duration of LN before biopsy, diffuse proliferative (class IV ± V) LN, complete remission, hypocomplementemia, and cyclophosphamide use as covariates (online suppl. Table 6). Cyclophosphamide use was intended as a surrogate representing differences in immunosuppressive treatments used for induction immunosuppression. None of the models accounting for sex differences in the above covariates resulted in a statistically significant association with the OR for the composite kidney outcome. In studies where men had lower odds of complete remission, men also tended to have higher odds of the composite kidney outcome approaching statistical significance ($p = 0.076$), though this finding was based on only four studies (Table 3).

Discussion

Kidney involvement remains one of the most important prognostic factors of poor outcome in patients with SLE. A recent meta-analysis suggested a 15-year risk of ESKD of 44% in patients with diffuse proliferative

Table 3. Meta-regression analysis for the effect of sex differences in the indicated characteristics on the OR for men versus women for the composite kidney outcome

Characteristics	exp(β_1)[b]	95% CI[c]	*p* value	Number of studies
MD in age	1.02	0.91, 1.14	0.8	10
MD in baseline creatinine	3.00	0.64, 14.1	0.2	7
MD in proteinuria	1.28	0.91, 1.80	0.2	7
MD in activity index	1.08	0.73, 1.57	0.7	6
MD in chronicity index	1.33	0.53, 3.34	0.5	6
MD in LN[a] disease duration	1.01	0.93, 1.10	0.9	4
OR diffuse proliferative LN (class IV±V)	1.15	0.92, 1.44	0.2	6
OR complete remission	0.13	0.01, 1.24	0.076	4
OR hypocomplementemia (low C3 or C4)	1.29	0.93, 1.80	0.13	4
OR cyclophosphamide use	1.08	0.96, 1.21	0.2	5

[a]Lupus nephritis. [b]β_1 regression coefficient for the indicated characteristic. [c]95% CI for exp(β_1).

LN [49]. Ethnicity, genetics, and sociodemographic factors have all been associated with a higher prevalence of LN and worse outcomes [50–52]. Sex appears to be another important factor, with some studies suggesting a higher incidence of kidney involvement and greater severity of disease in male patients with SLE [1, 2, 5]. Earlier observations have also linked male sex with worse kidney outcomes [29, 53, 54]. Using multivariate analysis, some recent studies found an independent association of male sex with adverse kidney outcomes [31, 37, 46], while others did not [28, 36, 44]. These inconsistencies may stem from differences in the follow-up, regional and ethnic differences among the diverse patient populations studied, and differences in the statistical adjustments applied to account for confounding variables. To address these inconsistencies, we systematically reviewed and synthesized the available data evaluating sex-based differences in the characteristics and outcomes of LN.

Our results showed that compared to women, men had a greater likelihood of class IV ± V LN. This association remained consistent on sensitivity analysis, and the strength of association was stronger when the analysis was restricted to studies that included more than 25 men. Men also had a higher mean Cr with an MD of 0.39 mg/dL, greater mean proteinuria of approximately 0.7 g/day, a lower mean serum albumin of 0.23 g/dL, and a greater likelihood of hypocomplementemia. Although the Cr was statistically significantly higher in men, the absolute difference between men and women (MD = 0.39 mg/dL) could be attributable to the expected physiological difference between sexes and may not necessarily reflect greater disease severity [55]. Assessment for a difference in estimated GFR between the sexes was not possible as this was reported by only a single study [39]. Our pooled analysis also demonstrated statistically significantly higher odds of worse kidney outcomes in men with LN (OR 2.20, 95% CI: 1.59–3.06). This association remained independent of differences in clinical characteristics at presentation by meta-regression analysis: namely serum Cr, proteinuria, hypocomplementemia, the presence of class IV ± V LN, and activity and chronicity index scores at diagnosis. We observed lower odds of complete remission and a greater risk of adverse kidney outcome in men compared to women by meta-regression, but these differences did not reach statistical significance (p = 0.076). These findings may be indicative of more severe disease at baseline in men but could also be attributable to between-sex differences in the choice of treatment or in treatment efficacy. The published data included in our systematic review and meta-regression were limited with respect to the choice of therapy and details on the treatment protocols. Specifically, while we were able to account for cyclophosphamide use as a covariate for meta-regression analysis, further details regarding the route of administration and cumulative dosage were not available. Hence, potential between-sex differences in the above could not be adjusted for and remain possible confounders. Regarding mycophenolate mofetil, only three of the included studies reported its use, as the rest of the studies likely antedate its adoption as a standard-of-care therapy for LN. To formally assess whether there are sex differences in response to certain treatments would require patient-level detailed data and the ability to adjust for baseline measures of disease severity. In the absence of a dedicated randomized clinical trial, this is conceivably feasible by a pooled analysis of patient-level data from completed randomized controlled studies in LN.

Several factors may underlie a propensity of male patients with LN toward more severe disease and worse kidney outcomes, although studies exploring the possible underlying mechanisms have shown mixed results. A study examining the sex-specific genetic effects of SLE susceptibility loci showed the risk of developing kidney disease to be double for men compared to women, and men had a significantly greater frequency of risk alleles in the HLA locus [56]. Conversely, animal studies suggest that exposure to estrogen accelerates autoantibody production and the development of immune-complex glomerulonephritis in lupus prone mice, while testosterone has a protective effect [57]. Additionally, karyotype studies suggest an X-chromosome dosage effect, as XXY males have a 14-fold greater risk of developing SLE compared to 46 XY males [58]. Studies of patients with chronic kidney disease have shown a more accelerated loss of kidney function and increased glomerular sclerosis in men compared to women [59]. Although the exact mechanisms remain elusive, interactions of androgens with the renin-angiotensin system, modulation of nitric oxide, and stimulation of pro-apoptotic pathways in kidney tubule cells have been postulated.

As SLE is disproportionately more common in women, this may lead to a cognitive bias among physicians causing delay in diagnosis of SLE in men who may then present with more advanced disease [60]. Sex differences in drug dosing, metabolism, tolerance, or adherence to the prescribed treatment are potential confounding factors that are poorly studied. In a recent multicenter observational study from China, men with LN were at greater risk of kidney failure despite a more frequent prescription of cyclophosphamide [61]. Another small case-control study from Brazil showed worse LN disease progression in men despite a trend toward a higher cumulative dose of cyclophosphamide compared to women (median [IQR] dose 9.6 g [3.0–12.3] vs. 4.8 g [1.8–9.6], respectively, p value = 0.06) [62].

Our findings highlight the importance of recognizing the increased likelihood of adverse outcomes in male patients with LN and the need to better understand and evaluate treatment efficacy specifically for this higher-risk patient population. Although men are reported to comprise only about 10% of patients with SLE [1], they accounted for 16–20% of patients with LN in recent multicenter cohorts [63, 64], consistent with the finding that men are at greater risk of developing LN than women. Furthermore, in recent large randomized controlled trials in LN leading to drug licensing, men accounted for only about 12% of participants in the BLISS-LN and AURORA1 trials (evaluating belimumab and voclosporin, respectively) [65, 66]. Our results suggest the need for better representation of male participants and attention to their balanced stratification in the treatment groups in future clinical trials. Whether men with LN would benefit from alternative, more intensive, or different combinations of immunotherapeutic agents than women is currently unknown. Our data suggest that increasing the awareness for a diagnosis for LN in men, screening for kidney disease in men with known SLE, and attentive monitoring for complications is warranted.

Our analysis has several strengths. We performed a systematic search of all major medical databases, and to our knowledge, this is the first systematic review and meta-analysis of studies evaluating the association between sex and outcomes in patients with biopsy-proven LN. We also quantitatively assessed this association, providing an estimate of the greater odds of adverse kidney outcomes in men with LN and also affirmed the direct and independent effect of sex towards this association by accounting for several covariates by meta-regression analysis. The latter was however limited by the small number of studies available to pool.

A major limitation of our analysis is the paucity of studies with adequate information regarding treatment factors. Only three of the 13 studies reporting kidney and mortality outcomes did not have significant treatment differences between men and women [28, 43, 44]. All of these studies were small, reporting outcomes for less than 50 men each, and there were important differences in clinical characteristics between the sexes in each cohort, including differences in Cr, proteinuria, and histopathologic features at presentation (details of risk of bias assessment are presented in online suppl. Table 7). Due to the small sample sizes and the presence of baseline clinical differences, a significant risk of bias likely remains. Furthermore, the question remains whether differences in treatment contributed to the observed difference in outcomes between men and women in our analysis. It should be noted that several studies included in our analysis likely antedate the use of mycophenolate mofetil, whereby treatment prior to its adoption as a standard-of-care for LN was primarily with either glucocorticoids or glucocorticoids plus cyclophosphamide. Because of this era effect in therapies (in comparing cyclophosphamide vs. mycophenolate), a pooled analysis of treatments would have been inappropriate. Where reported, there were no within-study differences in the proportions of patients treated with one agent versus another in all except one study [29]. This study included a small number of patients, and its exclusion from the pooled analysis did not alter the overall results.

As we had designed our search strategy to capture studies where the evaluation of sex differences was a specified objective, we excluded those studies that may have reported sex-based outcomes but were not designed to specifically assess sex differences in patients with LN. However, our findings are in agreement with large observational studies assessing outcomes of LN from Europe and China, where male sex was noted to be independently associated with kidney failure [61, 64, 67]. Other cohorts from India, Japan, and the UK did not observe this association, but all were small including less than 20 men each, limiting interpretation [68–70]. Additionally, we did not find evidence of significant publication bias in the studies included in our review for both the composite kidney outcome and mortality based on funnel plot inspection and Egger's regression analysis (online suppl. Figs. 27, 28).

Other limitations of our analysis include the retrospective nature of all included studies with a high degree of inherent bias, the majority of studies including small numbers of male patients, and the significant heterogeneity in the patient populations included in our analysis. This heterogeneity likely reflected differences in ethnic and socioeconomic backgrounds and clinical characteristics, as well as disparities in the structures and access to the health care systems from which they were derived. The majority of our data are comprised of cohorts from Asia, and further research involving male patients from other ethnicities is warranted to assess sex differences that may be specific to or differ in magnitude for certain ancestries.

In summary, our findings confirm the association between male sex and more severe disease as evidenced by worse kidney histopathology at presentation, lower odds of complete remission, and greater odds of kidney failure in men with LN. Differences in several covariates did not account for the independent association between sex and worse kidney outcomes when analyzed via meta-regression. Larger, long-term prospective studies are needed to validate this association and inform whether different, more proactive treatment strategies are required to improve outcomes for this higher risk patient population.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on the published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conception of research question: S.B.M. and P.H.N.; study design and conduct: S.B.M., M.A., D.M., W.L.S., and P.H.N.; statistical analyses: S.B.M., M.A., J.C., and A.B.; interpretation of results: all authors. All authors reviewed, revised, and approved the manuscript for submission.

Data Availability Statement

This study is based exclusively on the previously published literature. All data generated or analyzed in this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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