The Economic Burden of Lupus Nephritis: A Systematic Literature Review

Juliette C. Thompson · Anadi Mahajan · David A. Scott · Kerry Gairy

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ABSTRACT

Introduction: Few studies have evaluated the economic burden of lupus nephritis (LN). The aim of this systematic literature review (SLR) was to assess the economic burden (direct and indirect costs, and healthcare resource utilization [HCRU]) associated with LN, with particular focus on the burden of renal flares and end-stage kidney disease (ESKD).

Methods: This SLR (GSK study 213531) was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Searches of the MEDLINE and Embase databases were conducted for English language publications reporting cost or HCRU data in patients with LN (regardless of age or LN histological class) until December 10, 2019. Handsearching of conference proceedings and keyword-based searches in PubMed, Google, and Google Scholar were also conducted.

Results: Twenty-two studies were identified from 28 publications reporting the cost \( (n = 19) \) and HCRU \( (n = 13) \) associated with LN. Most studies were from North America \( (n = 13) \) and many used administrative claims data \( (n = 9) \). LN was associated with substantially higher direct costs (e.g., total annual, hospitalization, and ESKD-related direct costs), total indirect costs, and HCRU (e.g., hospitalization, outpatient services, and medication use) compared with patients without systemic lupus erythematosus (SLE) or non-renal SLE controls. ESKD and dialysis were significant contributors to economic burden. No studies described the cost of renal flares.

Conclusions: The consensus across the 22 studies was that the economic burden of LN is substantial, particularly in active or severe disease, or if there is progression to ESKD. Total direct cost may be underestimated in claims data given the challenges of identifying patients with LN. Further studies are vital to ascertain the cost of renal flares; a renal flare is likely to result in a period of increased HCRU, which could be mitigated by treatments that extend renal remission.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40744-021-00368-y.
**Keywords:** Cost; Economic burden; Lupus nephritis; Systematic literature review; Systemic lupus erythematosus

### Key Summary Points

The objective of this systematic literature review was to assess the economic burden (direct and indirect costs, and healthcare resource utilization [HCRU]) associated with lupus nephritis (LN), with a specific focus on the costs and HCRU associated with renal flares and end-stage kidney disease (ESKD).

LN was associated with substantially higher direct and indirect costs and HCRU compared with patients without systemic lupus erythematosus (SLE) or non-renal SLE control populations.

The largest gap in the literature is for HCRU and cost data characterizing a renal flare in patients with LN; a flare is likely to result in a period of increased HCRU and therefore optimal management and minimization of flares (i.e., maintaining renal remission) would reduce overall costs.

There are also limited cost and HCRU data on patients with LN and ESKD; presenting challenges for cost-effectiveness analysis where most data were derived from a non-SLE chronic kidney disease population.

### INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease that predominantly affects women of child-bearing age [1]. It is characterized by abnormal B-cell and T-cell activation and the generation of pathogenic autoantibodies [2, 3]. The resulting inflammation and subsequent damage of tissue and organs underpin the diverse range of debilitating clinical manifestations associated with the disease [3].

Approximately 31–48% of patients with SLE develop lupus nephritis (LN), the most severe organ manifestation of SLE, with 7–31% of patients being diagnosed with LN at SLE diagnosis [4–7]. Patients with LN have a higher risk of death compared with the general population, a risk that increases further if LN progresses to end-stage kidney disease (ESKD) [8]. Overall, up to 28% of patients with LN will subsequently develop ESKD, with a cumulative incidence ranging from 6–19% over 10 years [4]. Thus, the spectrum of LN includes patients with a range of clinical severities and therefore economic burden.

A single LN renal flare can reduce the glomerular filtration rate by approximately 40% and usually results in irreversible nephron loss that shortens kidney lifespan by decades [7]; as such, prevention of renal flares, or put conversely, the maintenance of renal remission, is a critical long-term treatment goal. As well as the clinical impact of renal damage, chronic kidney disease (CKD; not specific to LN) has been shown to significantly increase all-cause costs compared with those in patients without CKD [9]. This highlights the additional economic importance of preventing deterioration of renal function in LN. Patients with LN are also more likely to develop cardiovascular comorbidities than patients with SLE who do not have LN [10], which has been shown to increase the annual total costs of SLE by a factor of 2.3 [11]. Finally, risk of infection in SLE is increased by both disease activity (including renal involvement) and immunosuppressive treatment [7, 12]. Serious infections in SLE were found to increase hospitalization rates by up to 24 times compared with those in patients without SLE [13], which would likely result in substantially higher direct costs.

There is a high economic burden on the healthcare system associated with the management of patients with SLE, with mean annual direct and indirect cost ranges of...
US$2214–16,875 and US$2239–35,540, respectively [14, 15]. In patients with SLE, pharmaceutical costs accounted for 19–30% of total expenditures; and inpatient and outpatient costs composed 16–50% and 24–56% of overall costs, respectively [14]. However, higher costs have been reported for patients with LN [14, 16], with a mean annual direct cost range of US$29,034–$62,651 [14]. Increased disease activity and organ damage have also been shown to increase costs in patients with SLE [17–20]. Despite this, few studies have evaluated the economic burden of the subgroup of patients with LN.

Given the emergence of new treatments for LN [21, 22], there is a renewed need to evaluate and summarize the direct (e.g., hospitalization, outpatient visits, diagnostics, and medications) and indirect (e.g., lost productivity and absenteeism) costs and healthcare resource utilization (HCRU) associated with LN to inform efficient resource allocation in future clinical practice.

Accordingly, the objective of this systematic literature review (SLR) was to assess the economic burden associated with LN, with a particular focus on the costs and HCRU related to renal flares and ESKD.

We aimed to answer two specific research questions:

1. What are the direct and indirect costs associated with LN?
2. How does LN impact HCRU?

METHODS

Search strategy

In this study (GSK study 213531), a systematic literature search was conducted to identify publications reporting either cost or HCRU data in patients with LN (regardless of age, method of diagnosis, or LN histological class). Structured searches using indexed and free-text terms were conducted in MEDLINE and Embase from database inception to December 10, 2019. Both databases were searched via the Embase.com interface, using the specific disease and economic burden facets designed when developing the search strategy. The final search strategy is detailed in Supplementary Table 1. Handsearching of conferences proceedings (2017–2019) and keyword-based searches in PubMed, Google, and Google Scholar were also conducted to retrieve relevant evidence (Supplementary Methods).

Eligibility criteria and article selection

Screening of both title/abstract and full publication text was conducted by two independent reviewers in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23–25]; any disagreements were resolved by a third reviewer. Publications were included that met the predefined eligibility criteria summarized in Supplementary Table 2.

Data analysis and presentation

Direct and indirect costs associated with LN were stratified by disease stage and country, where possible. The impact of LN on HCRU was assessed by the frequency of hospitalizations and outpatient visits, and medication use. No quantitative synthesis was planned; the outcomes of this SLR are descriptive.

Ethics compliance

This article is an SLR of published articles and does not report a study conducted by the authors involving human participants or animals.

RESULTS

Study selection and characteristics

As shown in the PRISMA flow diagram (Fig. 1), 22 studies from 28 publications published between 2007 and 2019 were identified, which provided information on the cost (n = 19) and HCRU (n = 13) associated with LN [26–47].
Study characteristics (excluding cost-utility analyses [CUAs]) are detailed in Table 1. Studies were conducted primarily in North America (n = 13) and Asia (n = 7), with two conducted in Europe. There were 17 retrospective studies, one prospective cohort study associated with a cost prediction model and four CUAs. The three most common sources of data were claims databases (n = 9), observational studies (n = 5), and CUAs (n = 4). The sources of data for the four CUAs were a national database [40] and information from the literature [35, 41, 46]. Diagnostic criteria differed between studies and were not always reported. Where reported, the American College of Rheumatology (ACR) classification criteria was used, as were combinations of diagnosis codes of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and pathological classification from renal biopsy [48–50].

Characteristics of patients with LN

Patient characteristics were reported in 17 studies [26–34, 36, 38, 39, 42–45, 47]. The five studies not reporting patient characteristics were the four CUAs [35, 40, 41, 46] and one of the retrospective studies, which was only available as an abstract [37]. The included studies were primarily conducted in adults, with two studies conducted in children [32, 33], and three did not have an age restriction [29, 30, 34]. Patients were predominantly (> 70%) female.

Only four studies reported information on LN histological classification [28, 32, 36, 44]. Tse et al. [44] included only patients with Class IV, and Lateef et al. [36] included mainly patients with Class IV (57.1%). Most patients included in the study by Guerra et al. [32] had Class IV or V (73.7%) nephritis. Barbour et al. [28] stratified per-patient medication costs by LN class but did not report the proportions of patients in each class.

Only four studies reported LN activity [26, 29, 32, 46], one of which included only active patients [46]. One study included 37.6% active (defined as a SLE Disease Activity Index 2000 [SLEDAI-2 K] score > 6) and 18.4% inactive disease in patients with LN [26].
| First author, year | Study design | Country | Data collection period (analysis period/follow-up) | Patient population | LN diagnostic criteria | Populations compared |
|-------------------|--------------|---------|---------------------------------------------------|--------------------|-----------------------|---------------------|
| Carls et al. [29](2009) | Case–control claims database analysis | USA | 2000–2004 (1 year) | Patients with SLE (≥ 1 SLE inpatient claim or ≥ 2 SLE outpatient claims ≥ 30 days apart). Newly active patients with SLE selected | Nephritis ICD-9-CM codes | LN vs. SLE without LN vs. matched control patients without SLE |
| Li et al. [38] (2009) | Retrospective claims database analysis | USA | 1999–2005 (5 years) | Patients with SLE (ICD-9-CM diagnosis code, or ≥ 2 SLE outpatient claims during office visit and/or ED visit ≥ 30 days apart; Medicaid population) | Nephritis ICD-9-CM codes | LN vs. SLE without LN vs. matched patients without SLE |
| Pelletier et al. [42] (2009) | Retrospective claims database analysis | USA | 2007 (1 year) | Patients with SLE (2 continuous claims ICD-9-CM.710.0; including patients with Medicaid and Medicare) | ≥ 1 claim indicative of renal involvement, with ≥ 2 claims for SLE (ICD-9-CM codes) | LN vs. SLE without LN |
| Tse et al. [44] (2009) | Retrospective observational study, cost source NR | Hong Kong | NR (2 years) | Patients with diffuse proliferative LN Biopsy; Class IV (WHO) | | CTX-AZA vs. MMF |
| Lateef et al. [36] (2010) | Retrospective observational study | Singapore | 2005–2008 (median: 28 months) | Patients with SLE (ACR criteria who had received rituximab for treatment of severe, refractory disease | ACR; confirmed on histopathology | NA |
Table 1 continued

| First author, year | Study design | Country | Data collection period (analysis period/follow-up) | Patient population | LN diagnostic criteria | Populations compared |
|-------------------|--------------|---------|---------------------------------------------------|---------------------|-----------------------|----------------------|
| Aghdassi et al. [26](2011) | Patient survey, costs from various sources | Canada | 2004–2009 (NA) | Patients with SLE (at least 4/11 ACR criteria) attending tertiary specialist clinic | LN defined by histological findings on renal biopsies or by laboratory abnormalities; proteinuria > 0.5 g/24 h and/or presence of urinary cellular casts ever | LN vs. SLE without LN Active LN vs. inactive LN |
| Hiraki et al. [33](2012) | Retrospective claims database analysis | USA | 2000–2004 (NR) | Patients in the Medicaid Analytic eXtract (MAX) database aged 3 to < 18 years with SLE (≥ 3 ICD-9 codes of SLE [710.0], each ≥ 30 days apart) | NR | NA |
| Furst et al. [31](2013) | Case–control claims database analysis | USA | 2003–2008 (NR) | Patients with SLE (ICD-9-CM 710.0x, with evidence of ≥ 1 inpatient claim or ≥ 2 ED visits ≥ 30 days apart; Medicaid and Medicare population) | ICD-9-CM codes | LN vs. matched controls without SLE |
| Yeh et al. [47](2013) | Retrospective claims database analysis | USA | 2004–2011 (1 year) | Patients with SLE (ICD-9 code 710.0 from ≥ 2 outpatient or ≥ 1 inpatient claims) | NR | Cohorts defined by number of renal diagnoses |
| First author, year | Study design | Country | Data collection period (analysis period/follow-up) | Patient population | LN diagnostic criteria | Populations compared |
|-------------------|--------------|---------|---------------------------------------------------|-------------------|------------------------|---------------------|
| Jönsen et al. [34](2016) | Retrospective registry analysis, costs from The Medicines Compendium | Sweden | 2003–2010 (8 years) | Patients with SLE (confirmed diagnosis and enrollment in a registry before or during study period) | ACR-SLICC-DI (manifestation of glomerulonephritis) | LN vs. SLE (total population including LN) |
| McCormick et al. [39](2016) | Retrospective claims database analysis | Canada | 1996–2010 (19,139 patient years) | Patients with incident SLE from BC during 1996–2010 (no prior SLE diagnosis from 1990–1995) | Primary (narrow) definition: > 2 renal-coded encounters AND > 2 nephrologist visits | Secondary (broad) definition: > 2 renal encounters OR > 2 nephrologist visits |
| Li [37](2017) | Retrospective observational study, cost source NR | China | 2014–2015 (NR) | Patients with LN | Primary LN diagnosis from electronic medical records system | NA |
| Venegas et al. [45](2017) | Patient survey, cost source NR | Philippines | 2016 (NA) | Patients with SLE > 18 years with a minimum 1-year follow up consecutively seen at Lupus Clinics | NR | LN vs. SLE without LN |
| First author, Study design  | Country                  | Data collection period (analysis period/follow-up) | Patient population                                                                 | LN diagnostic criteria                                                                 | Populations compared                |
|-----------------------------|--------------------------|-----------------------------------------------------|------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-------------------------------------|
| Barber et al. [27] (2018)   | US, Europe, Canada, Mexico, Korea | 1999–2013 (mean 6.3 years)                           | Patients with SLE from the SLICC network (fulfilling ACR revised classification criteria for SLE and enrolled into an inception cohort within 15 months of diagnosis) | Renal biopsy or fulfillment of the renal item on ACR criteria                          | LN vs. patients with SLE without LN |
| Barbour et al. [28] (2018)  | Canada                   | 2000–2012 (mean 6.8 years)                           | Patients with LN                                                                  | Renal biopsy                                                                           | NA                                  |
| Feldman et al. [30] (2018)  | USA                      | 2000–2010 (mean 3.1 years)                           | Patients aged 5–65 years with SLE (≥ 3 SLE claims; Medicaid population)            | ≥ 2 LN claims (ICD-9-CM codes: glomerulonephritis, renal failure, or nephrotic syndrome) | Male vs. female                     |
| Guerra et al. [32] (2018)   | USA                      | 2008–2017 (30 days)                                  | Newly diagnosed pediatric patients with LN (including patients with Medicaid)       | NR                                                                                     | Early readmitted to hospital group (< 30 days) vs. not early readmitted group |
| First author, year | Study design | Country | Data collection period (analysis period/follow-up) | Patient population | LN diagnostic criteria | Populations compared |
|-------------------|--------------|---------|---------------------------------------------------|--------------------|-----------------------|----------------------|
| Tanaka et al. [43] (2018) | Retrospective claims database analysis | Japan | 2010–2012 (3 years) | Patients selected from the JMDC-CDB, aged 15–65 years and a SLE-related visit (ICD-10-M32) with continuous inclusion eligibility for 6 months prior and 3 years post-index date | Combined elements of SLEDAI, SLAM, and BILAG criteria, with use of SLE medications and consensus clinical opinion | NP/LN vs. SLE without NP/LN |

* ICD-9-CM codes for acute glomerulonephritis, nephrotic syndrome, chronic glomerulonephritis, nephritis not otherwise specified, acute renal failure, CKD, renal failure unspecified, kidney biopsy, hemodialysis, or peritoneal dialysis, kidney transplant

ACR American College of Rheumatology, ACR-SLICC-DI American College of Rheumatology-Systemic Lupus International Collaborating Clinics–Damage index, AZA azathioprine, BC British Columbia, BILAG British Isles Lupus Assessment Group index, CKD chronic kidney disease,CTX cyclophosphamide, CTX-AZA cyclophosphamide induction followed by azathioprine maintenance, CUA cost-utility analysis, ED emergency department, eGFR estimated glomerular filtration rate, HCRU healthcare resource utilization, ICD-9 International Classification of Diseases, Ninth Revision, ICD-9-CM International Classification of Diseases, Ninth Revision, Clinical Modification, ICD-10-M32 International Classification of Diseases, Tenth Revision, systemic lupus erythematosus, JMDC-CDB Japanese Medical Data Center Claims Database, LN lupus nephritis, MMF mycophenolate mofetil, NA not applicable, NERG not early readmittance group, NP neuropsychiatric, NR not reported, SLAM Systemic Lupus Activity Measure, SLE systemic lupus erythematosus, SLEDAI Systemic Lupus Erythematosus Disease Activity Index, SLICC Systemic Lupus International Collaborating Clinics American College of Rheumatology Damage index, SLR systematic literature review, UK United Kingdom, USA United States of America, US United States, WHO World Health Organization
Few studies reported inclusion of patients with either CKD complications or ESKD. A Canadian study by Barbour et al. [28] and a US study by Li et al. [38] reported that 13.3% of patients with LN and 6.8% of patients with SLE had ESKD, respectively. A further US study by Feldman et al. [30] reported the 5-year cumulative incidence of ESKD to be 22.3% in males and 21.2% in females with LN.

**Direct costs**

Direct costs reported in the identified studies included the cost of hospitalization, outpatient visits/services, emergency department (ED) visits, diagnostic tests, medications, alternative treatments, assistive devices, and surgical procedures (Table 2).

Total costs for LN [29, 31, 34, 38, 42, 43] were consistently higher than comparator populations; both patients without SLE [29, 31] and patients with SLE without LN (Table 2) [34, 38, 42, 43]. In two studies, the increase in total annual costs observed in the LN population versus the matched controls without SLE was significant ($p < 0.001$) [29, 31]. The total costs reported by Carls et al. [29] were higher than other claims studies conducted in the US. The authors hypothesized that expenditure was based on actual experience of patients rather than relying on national- or country-specific estimates based on negotiated fee schedules, which is often the case in other claims database analyses.

Two cost-analyses conducted in the US and Canada compared different algorithms to identify LN from claims databases [39, 47]. In the US study [47], costs were higher with increased number of renal diagnoses (US$33,176 with ≥1 renal diagnosis, US$38,883 with ≥3 renal diagnoses plus ≥3 nephrologist visits). Similarly, in the Canadian study [39], the more stringent LN definition of ≥2 renal-coded visits AND ≥2 nephrologist visits resulted in higher unadjusted mean per-patient-year costs for patients with LN than when LN was defined as ≥2 renal-coded visits OR ≥2 nephrologist visits (CA$85,292 vs. CA$70,538, respectively). These data indicate that the stringency of codes used to identify a patient with LN has an impact on the reported costs.

Two other Canadian studies stratified costs by LN classification and severity [27, 28]. Barbour et al. [28] reported a significant increase in annual per-patient total costs in patients with Class III or IV (≥V) LN disease (Year 2000: CA$209, Year 2013: CA$1592; 2016 CA$; $p < 0.001$). In patients with Class V LN alone, costs increased over the same time period, but this was not significant (CA$118, CA$1002; $p = 0.016$). Using prospectively collected data from the Systemic Lupus International Collaborating Clinics (SLICC) network inception cohort, Barber et al. [27] used a multistate Markov model to predict mean annual costs per patient in health states defined by the presence of LN and by either worsening estimated glomerular filtration rate (eGFR) or increasing estimated proteinuria. The model showed increasing costs in patients with LN and/or with worse renal function, versus those without LN or with eGFR > 60 ml/min. Conversely, when Aghdassi et al. [26] compared patients with SLE with or without LN, and active (defined as a SLEDAI-2K score > 6) and inactive disease, there was no difference in annual costs between LN and patients with SLE without LN regardless of activity, but there was a significant difference in total annual costs between active and inactive LN ($p < 0.05$).

In several studies, an increase in annual hospitalization costs was observed between patients with LN and their matched control patients without SLE, the total SLE population or patients with SLE without LN [29, 34, 42]. However, in a Canadian study by Aghdassi et al. [26], hospitalization costs were slightly higher for patients with SLE without LN compared with patients with LN, and this difference was not significant.

No studies provided information about costs associated with renal flares specifically in patients with LN; however, Tanaka et al. [43] reported the cost of SLE flares (Table 2).

Costs for ESKD and its treatment were reported in six studies (Tables 2 and 3) [27, 35, 38, 40, 41, 45], three of which were CUA [35, 40, 41]. In the US study by Li et al. [38], median annual medical costs for patients with SLE and ESKD increased by twofold between Year 1 and Year 5 (US$33,827–66,490), whereas...
| Author year, country (currency year, currency) | Period | Patients with LN, N | Comparison | Cost category | Cost results (USD) | p value |
|-----------------------------------------------|--------|---------------------|------------|---------------|-------------------|---------|
| Carls 2009 [29], USA (2005 USD) 2000–2004 592 |        | Patients with LN vs. | Mean (SD) total medical expenditure in 12-month study period | 58,389 (99,483) 11,527 (21,935) | < 0.001 |
| Li 2009 [38], USA (2006 USD) 1999–2005 489 |        | Patients with LN vs. | Mean (median) annual medical costs per patient at year 5 | 50,578 (21,500) 16,638 (8,496) | NA |
| Pelletier 2009 [42], USA (2008 USD) 2007 1068 |        | Patients with LN vs. | Total mean (SD) annual costs; SLE-related mean costs | 30,652 (51,746); 6981 (15,576) 12,029 (26,577); 2489 (11,194) | N/A |
| Aghdassi 2011 [26], Canada (CAD)$^*$ 2004–2009 79 |        | Patients with LN vs. | Mean (SD) total cost/4 weeks; Mean (SD) annual cost | 969 (765); 12,597 (9946) 814 (1011); 10,585 (13,149) | < 0.05 |
| |        | Patients with active LN vs. inactive LN | 1094 (790); 14,224 (10,265) 703 (648); 9142 (8419) | < 0.05 | < 0.05 |
Table 2 continued

| Author year, country (currency year, currency) | Period | Patients with LN, N | Comparison | Cost category | Cost results (USD) | p value |
|-----------------------------------------------|--------|---------------------|------------|---------------|-------------------|---------|
| Furst 2013 [31], USA (2009 USD)               | 2003–2008 | 907 | Patients with LN vs. Matched patients without SLE | Overall mean (95% CI) annual costs in 12-month post-index period | 33,472 (29,797–37,146) vs. 5347 (4719–5976) | < 0.001 |
| Yeh 2013 [47], USA (USD)                      | 2004–2011 | 24,357 | Patients with differing numbers of renal diagnoses: ≥ 1 renal diagnosis ≥ 2 renal diagnoses ≥ 3 renal diagnoses ≥ 3 renal diagnoses plus ≥ 3 nephrologist visits | Annual medical costs | NA |
| Jönsson 2016 [34], Sweden (2011 USD)          | 2003–2010 | 321 | Patients with LN vs. Patients with SLE without LN | Mean (SD) total direct cost; median (IQR) total direct cost | 14,190 (35,756); 4709 (1661–10,989) vs. 10,188 (28,352); 2860 (1153–7708) | NA |
| McCormick 2016 [39], Canada (2010 CAD)        | 1996–2010 | 303/632 | > 2 renal AND > 2 nephrologist visits LN vs. Patients with SLE without LN | Unadjusted 5-year mean per-patient-year costs | 85,292 vs. 33,022 vs. 27,487 | < 0.01 |
| Venegas 2017 [45], Philippines (2016 Philippine peso) | 2016 | 166 | Patients with SLE requiring dialysis vs. Patients with LN without dialysis vs. Patients with SLE without LN | Annual cost | 595,400 vs. 144,700 vs. 55,020 | < 0.001 |
| Author year, country (currency year, currency) | Period | Patients with LN, N | Comparison | Cost category | Cost results (USD) | p value |
|---------------------------------------------|--------|---------------------|------------|---------------|-------------------|---------|
| Tanaka 2018 [43], Japan (USD)              | 2010–2012 | 110               | Patients with NP lupus/LN vs. Patients with SLE without NP lupus/LN | Mean (SD) total costs over the 3-year study period | 39,976 (47,563) vs. 22,500 (36,128) | 0.0004 |
| Worsening eGFR                              |        |                    |            |               |                   |         |
| Barber 2018 [27], Multiple (2015 CAD)      | 1999–2013 | 609               | Patients stratified by LN status and state of eGFR: Predicted annual health costs, mean (95% CI) |                       | NA |
| State 1 (LN)                               |        |                   |            |               | 3858 (2858–4859) |         |
| State 2 (LN)                               |        |                   |            |               | 4012 (2362–5662) |         |
| State 3 (LN)                               |        |                   |            |               | 20,837 (3628–38,046) |         |
| ESKD                                       |        |                   |            |               | 51,313 |         |
| vs.                                        |        |                   |            |               |                   |         |
| State 1 (no LN)                            |        |                   |            |               | 1813 (1034–2593) |         |
| State 2/3 (no LN)                          |        |                   |            |               | 2955 (37–5873) |         |
| Barbour 2018 [28], Canada (2016 CA$)       | 2000–2012 | 362               | Patients with LN class III or IV (± V) vs. Patients with LN class V disease | Annual per-patient cost | 209 (year 2000) vs. 1592 (year 2013) | < 0.001 |
| a Disease activity was determined using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2 K). SLEDAI > 6 was considered an active disease. b USA, n = 426; Europe, n = 405; Canada, n = 372; Mexico, n = 184; and Korea, n = 158. 

CAD Canadian dollars, CI confidence interval, eGFR estimated glomerular filtration rate, ESKD end-stage kidney disease, IQR interquartile range, IV intravenous, LN lupus nephritis, NA not applicable, NP neuropsychiatric, SD standard deviation, SLE systemic lupus erythematosus, USD United States of America, USD US dollars
costs for patients with LN without ESKD increased by approximately 1.2-fold in the same time period (US$10,053–11,532). Similarly, Venegas et al. [45] found that treatment costs were significantly increased in patients with SLE requiring dialysis, versus patients with LN who did not require dialysis versus patients with SLE without LN (2016 Philippine peso 595,400 vs. 144,700 vs. 55,020, respectively; \( p < 0.001 \)); ESKD was also found to be a significant independent contributor to treatment costs \( (p < 0.001) \).

In addition, Barber et al. [27] reported that predicted mean annual costs related to ESKD were more than 17-fold higher than health states reflecting good renal function.

### Indirect costs

Indirect costs reported in the identified studies included the cost of absenteeism (absence from work), disability, and other loss of productivity (for patient and caregiver) (Table 4).

Four studies reported indirect costs, including cost of loss of productivity (for patient and caregiver) [40, 41], cost of absenteeism and short-term disability [29], and total indirect costs [34]. In the Swedish study by Jönsen et al. [34], although higher indirect costs were reported for the LN cohort compared with the total SLE cohort (mean [SD]: 2011 US$25,094 [31,387] vs. US$23,181 [30,792]), the difference was not significant. Overall, no significant differences in indirect costs between patients with LN and comparators were reported (Table 4).

In the Canadian study by Aghdassi et al. [26], 48.1% of patients with LN versus 45.2% of patients with SLE without LN were employed. Of these, more patients with LN (56.8%) missed work compared with patients with SLE without LN (42.9%) and had more days of missed work in the past month (8.5 vs. 4.1, respectively). Furthermore, caregivers of patients with LN missed more hours of work than those caring for patients with SLE without LN \( (p < 0.05) \).

### HCRU

Overall, patients with LN required more inpatient, outpatient, and ED visits, were more likely to be hospitalized, spend longer in hospital, and need more medication than patients with SLE without LN or patients without SLE [26, 31, 38, 39, 42].

The mean annual numbers of inpatient, outpatient, and ED visits were higher for patients with LN (inpatient: 0.6–1.0, outpatient: 6.6–7.4, ED: 1.5–1.9) compared with the total SLE population (inpatient: 0.3–0.5, outpatient: 5.6–6.9, ED: 1.3–1.6) or patients without SLE (inpatient: 0.1–0.2, outpatient: 3.4–3.8, ED: 0.5–0.9) [31, 38, 42]. In addition, the mean annual numbers of inpatient, outpatient, and ED visits were higher in pediatric patients with LN (in the months prior to ESKD) (inpatient: 2.4, outpatient: 10.8, ED: 2.0) compared with adult patients with LN (inpatient: 0.6–1.0, outpatient: 6.6–7.4, ED: 1.5–1.9) [31, 33, 38]. Feldman et al. [30] reported that male patients with LN had fewer outpatient visits (incidence rate ratio [IRR], 95% confidence interval [95% CI] 0.88, 0.80-0.97) and fewer ED visits (IRR, 95% CI 0.75, 0.63–0.90) than female patients with LN.

The proportion of patients reporting inpatient hospitalizations increased by 1.3–2.2 times in patients with LN compared with patients with SLE without LN [26, 38, 39, 42] and by 3.7–5.3 times compared with matched control patients without SLE [31, 38]. Pelletier et al. [42] also reported that patients with LN had longer lengths of stay compared with patients with SLE without LN (16.52 vs. 9.69 days, \( p < 0.001 \)). However, this was not that case in the Canadian analysis by Aghdassi et al. [26] (2.8 vs. 5.7 days; \( p \geq 0.05 \)). Patients with active LN were more likely to be hospitalized than those with inactive LN (7.8 vs. 3.8%), but patients with inactive LN spent longer in hospital than those with active LN (4.0 vs. 2.5 days). In a study conducted in Singapore, the length of hospitalization was significantly longer before versus after treatment with rituximab \( (p = 0.027) \) [36], while in an analysis conducted in Hong Kong, the duration of hospitalization was longer in patients with LN treated with sequential cyclophosphamide (CYC) induction followed by azathioprine maintenance compared with patients treated with mycophenolate mofetil (MMF) (mean [SD] 6.2 [18.2] vs. 1.1 [2.8] days) [44].

Over the 13-year period analyzed in Barbour et al. [28], the use of rituximab (from 0 to 3.5%),
| Author year, country (currency year, currency) | Patient population and patients compared | Sources of data | Cost category | Cost results (USD) |
|---------------------------------------------|----------------------------------------|----------------|---------------|--------------------|
| Wilson 2007 [46], UK (2005 GBP)            | Patients with active LN requiring induction therapy MMF vs. IV CYC | A SLR of the literature identified two studies comparing MMF and IV CYC, reporting results following induction therapy [59, 60] Further data was extracted from a Cochrane review of all treatments [61] | Total mean costs per 12 weeks (including medication, secondary care activity, and other monitoring): | MMF: 843.25 IV CYC: 1754.54 No immunosuppressive therapy: 90.83 |
| Mohara 2014 [40], Thailand (2012 Thai Baht) | Patients with newly diagnosed severe LN receiving induction and maintenance therapy Four treatment regimes | The PubMed database was searched using the following keywords: (lupus nephritis [MeSH]) AND (cyclophosphamide [MeSH] OR azathioprine [MeSH] OR mycophenolic acid [MeSH]) Only articles published between January 2000 and July 2012 that were written in English, Spanish, or Thai were considered. Study types that were considered included controlled clinical trials, randomized controlled trials, clinical trials, and comparative studies Ten studies met the inclusion criteria by giving details of the dosage of the drugs under consideration and examined the treatment outcomes for any of the five defined health states Costs sourced from national databases HCRU estimated from a medical record review on LN treatment at four tertiary care hospitals (laboratory tests and drug administrative costs) | Mean (SE) cost of dialysis for patients with end-stage renal failure (per year) | 497,019 (4998) |
| Author year, country (currency year, currency) | Patient population and patients compared | Sources of data | Cost category | Cost results (USD) |
|-----------------------------------------------|------------------------------------------|----------------|---------------|-------------------|
| Nee 2015 [41], USA (2013 US$) | Patients with proliferative LN receiving maintenance therapy | A Cochrane meta-analysis of maintenance therapy with MMF vs. AZA was performed using data from three clinical trials (MAINTAIN, ALMS, and Contreras’s study) and Red Book, and was the foundation of this base-case model | Mean costs (range) over 1 year | Remission (nonpharmaceuticala): 3368.34 (1263.13–2105.21) Relapse (nonpharmaceuticala): 6486.85 (2432.57–4054.29) |
| Kim 2019 [35], China (Chinese Yuan) | Patients with moderate-to-severe LN requiring induction therapy | Three CUAs were identified and assessed from the SLR: Four different treatment regimens combining IV CYC, AZA, and MMF for long-term therapy in Thailand [40] MMF and AZA as maintenance treatments from a US perspective [41] MMF and IV CYC as induction treatments from a UK perspective [46] | Medical costs of all patients in the ESKD state (per year) | 80,188 |

*a Care provided by specialists, nonspecialists, nonphysician healthcare professionals, laboratory studies, imaging studies, emergency room visits, outpatient surgery, and hospitalizations
ALMS Aspreva Lupus Management Study, AZA azathioprine, CYC cyclophosphamide, CUA cost–utility analysis, ESKD end-stage kidney disease, GBP pound sterling, HCRU healthcare resource utilization, IV intravenous, LN lupus nephritis, MeSH Medical Subject Headings, MMF mycophenolate mofetil, NR not reported, SE standard error, SLR systematic literature review, UK United Kingdom, USA United States of America, US United States, US$ US dollar
calcineurin inhibitor (from 0 to 4.5%), and MMF (from 3.3 to 55.3%) for treatment of LN all increased from the year 2000 to 2013. Patients with LN also averaged 128.6 more dispensed prescriptions than patients with SLE without LN over 5 years [39].

**DISCUSSION**

This SLR included 22 studies from 28 articles published between 2007 and 2019 that provided information on the cost and HCRU associated with LN.

LN was associated with substantially higher direct costs compared with patients without SLE or patients with SLE without LN [26–29, 31, 34, 37–39, 42, 43, 45, 47]. Direct healthcare costs were 1.2–3.0 times greater in patients with LN versus patients with SLE without LN [26, 34, 38, 42, 43, 45]. As expected, differences were greater (5.1–6.3 times) when comparisons were made between patients with LN and matched control patients without SLE [29, 31].

Costs for patients with ESKD were higher than for patients with LN who had not progressed to ESKD [38]. The need for dialysis significantly increased the cost of treatment (4.1 times) compared with patients with LN not requiring dialysis, and ESKD was a significant independent contributor to treatment costs [45]. In addition, Barber et al. [27] reported that increased costs were associated with worsening eGFR, with a marked increase among patients with LN reaching < 30 ml/min eGFR without ESKD. This trend is observed in studies of CKD due to other causes [9, 51], and reflects the importance of preventing any deterioration of renal function including prior to reaching kidney failure.

Barbour et al. [28] previously reported that costs of immunosuppressive treatments for glomerulonephritis were increasing over time due to changing patterns in clinical practice. In particular, the Aspreva Lupus Management Study (ALMS) reported pivotal data for LN treatment in 2009 and 2011, which likely consolidated the use of MMF as standard therapy for LN, especially in the US and Europe [52, 53].

These changes in clinical practice over the study period (2007–2019) may have influenced the direct costs of LN and make it more difficult to compare costs between studies.

Indirect costs were infrequently reported and no significant differences were observed between patients with LN and comparators [29, 34, 40, 41]. Although SLE tends to affect patients during their most productive years of life, in terms of professional and familial achievement [1], there was limited information on the degree of productivity lost among patients with LN. Further research is also needed to understand the impact of LN on health-related quality of life and activities of daily living, which in turn may impact productivity. Only one of the studies included in this analysis reported limited data on absenteeism/presenteeism in LN [29], a substantial contributor to lost productivity among patients with SLE. A full understanding of indirect costs (notably productivity) is a particular gap in the literature and a future area of research.

In most of the included studies, patients with LN were more likely to be hospitalized and spend longer in hospital than their comparators [26, 31, 32, 39, 42, 43]. However, Aghdassi et al. [26] found that patients with SLE alone spent longer in hospitals than patients with active LN. This observation could be due to the more intensive treatment required for SLE, when extrarenal manifestations are severe, compared with LN. In addition, pediatric patients with LN (in the months prior to ESKD) were found to have more inpatient, outpatient, and ED visits than adult patients with LN [31, 33, 38]. This could suggest that pediatric patients would have higher HCRU costs than adult patients with LN.

Patients with LN were also more likely to require outpatient visits and a greater quantity of medication than their comparators [26, 28, 31, 38, 42], particularly immunosuppressants and corticosteroids [42, 43]. As new treatments for LN emerge, it is important to understand the relationship between medication use and HCRU for cost-effectiveness studies. Evidence suggests that there is a cost-saving potential of earlier aggressive therapy to prevent disease progression. Despite the higher initial costs of biologics compared with standard
| Author, year, country (currency year, currency) | Study details | Indirect cost category | Results |
|---------------------------------------------|---------------|------------------------|---------|
| Carls 2009 [29] USA (2005 USD)              | Case–control claims database analysis, 2000–2004 | Mean (SD) costs during 12-month study period | LN: Absenteeism ($n = 10, 70.0\%$ claimed): 4781 (10,144), $p = 0.946$ vs. LN vs. SLE: 44.4 vs. 47.1 years; Short-term disability ($n = 20, 15.0\%$ claimed): 1025 (2673), $p = 0.375$ vs. Matched control patients without SLE: Absenteeism ($n = 10, 100\%$ claimed): 4552 (2878); Short-term disability ($n = 20, 5.0\%$ claimed): 386 (1728) |
| Mohara 2014 [40] Thailand (2012 Thai Baht) | CUA/SLR | Productivity loss$^a$ of patient and caregiver per visit, mean (SE) | LN: 176 (49) Major infection per episode: 5739 (982) |
| Nee 2015 [41] USA (2013 USD)                | CUA/SLR | 6-month/12-month mean costs of productivity loss (range) due to$^b$: Remission: 8033.19/16,066.38 (6024.89–10,041.49) Relapse: 8564.07/17,128.13 (6423.05–10,705.09) | |
| Jönsen 2016 [34] Sweden (2011 USD)         | Retrospective registry analysis, 2003–2010 | Mean (SD)/median (IQR) costs$^c$ | LN: 23,181 (30,792)/0 vs. SLE: 25,094 (31,387)/1255 (0–53,744) |

$^a$ Due to sick leave. $^b$Time lost from labor and non-labor (i.e., household work) market activity, plus the time that a caregiver spent helping the patient receiving healthcare services and the time the caregiver spent doing housework. $^c$Based on sickness leave and disability pensions. CI confidence interval, CUA cost–utility analysis, IQR interquartile range, LN lupus nephritis, SD standard deviation, SE standard error, SLE systemic lupus erythematosus, SLR systematic literature review, USA United States of America, USD United States dollars.
therapies, rituximab has been found to be cost
saving in the treatment of LN, as cost and
number of hospitalizations are decreased after
treatment [36].

This SLR has several limitations. As the
search was performed in 2019 relevant recent
publications could have been missed. For
example, Padiyar et al. [54] has recently
reported a comparison of the costs of oral CYC
compared with intravenous CYC and Bell et al.
[55] recently published an abstract reporting the
burden of illness in LN; it was reported that
patients with LN have significantly higher
ambulatory visits, ED visits, hospitalizations,
and costs than patients without SLE. Miyazaki
et al. [56] also recently reported HCRU of
patients with LN compared with patients with-
out central nervous system (CNS) lupus or LN; a
higher proportion of patients with LN had ≥ 1
hospitalization compared with patients without
CNS lupus or LN.

The method of LN case ascertainment also
differed between the included studies. Nine of
the 22 studies included in this SLR derived data
from claims databases, which are inherently
reliant on accurate coding of medical condi-
tions. The identification of patients from
administrative claims data, particularly if a
disease does not have a specific ICD diagnostic
code, necessitates the use of proxies for diag-
nosis. For example, diagnosis of LN was
assumed if patients had concurrent codes for
SLE and renal disease. Notably, two studies
included in this review demonstrated that the
increasing stringency of diagnosis code
algorithms used to identify patients with LN
resulted in an increase in the reported costs
[39, 47].

In some studies, data were taken from claims
databases of employed individuals, meaning
patients not in work were not captured. This
can introduce bias as analyses are consequently
conducted on a “healthier” population with
milder SLE who are able to work, rather than the
general SLE population; this may particularly
affect estimates generated for patients with LN
given that it is the severe form of the disease.
However, several studies using Medicare and
Medicaid databases were also included in this
study. Therefore, the potential bias introduced
by claims databases may not have such an effect
on this analysis.

In the US healthcare system, the cost of care
for patients with ESKD is funded almost entirely
by Medicare [38, 57]; hence, the costs associated
with dialysis, kidney transplant, and associated
medications will be underestimated by claims
analyses that do not include all claims paid by
Medicare. Given the high per-patient cost of
dialysis and kidney transplant, this may have an
important impact on the estimation of eco-
nomic burden of LN.

As the search included in this study focused
on the subgroup of patients with LN, relevant
aspects of economic burden borne by the
broader SLE population, such as productivity
losses, may not be reflected. For example, the
claims data analysis by Garris et al. [58] was not
included in the present SLR as cost data specific
to an LN population was required to be included
in the study.

The clear absence of data on the cost asso-
ciated with a flare in SLE generally, but partic-
ularly with a renal flare, is a notable knowledge
gap in the current literature. Although it is
likely that the cost of flare is incorporated into
other costs reported, without explicit data
describing flare costs it is difficult to determine
the immediate economic impact if these
important clinical events can be avoided. Simi-
larly, there are limited data available describing
patients with LN with ESKD, with data used in
published cost-effectiveness analyses coming
from the general ESKD population rather than
LN-related ESKD. As new interventions emerge
for the treatment of active LN, greater delin-
eation of these costs at the patient level will be
critical to demonstrating their economic value.
CONCLUSIONS

There is consensus across the studies included in this SLR that LN is expensive to manage. Specifically, LN was associated with higher direct costs (including total annual costs and costs of hospitalization and ESKD), total indirect costs, and HCRU (including hospitalization, outpatient services, and medication use) compared with those of either patients without SLE or patients with SLE without LN. However, limitations of current studies mean that it is difficult to determine the true cost of illness associated with LN. The greatest gap in the literature, which should be prioritized as a future research priority, is the absence of specific data for the cost of renal flare in patients with LN, despite it being a clinically important and frequently occurring medical emergency. As a disease flare is likely to result in a period of intense resource use for a patient with SLE, minimization of flare recurrence should reduce overall costs associated with LN disease control.

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**Compliance with Ethics Guidelines.** This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

**Data Availability.** All data generated or analyzed during this study are available in this published article or as supplementary information files.

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