Healthcare Cost and Loss of Productivity in a Canadian Population of Patients with and without Lupus Nephritis

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ABSTRACT. ***Objective.*** To compare the healthcare cost and loss of productivity in patients with systemic lupus erythematosus (SLE) with (LN) and without lupus nephritis (lupus nephritis-negative, LNN).

Method. Patients were classified into those with active (ALN and ALNN) and inactive disease (ILN and ILNN). Patients reported on visits to healthcare professionals and use of diagnostic tests, medications, assistive devices, alternative treatments, hospital emergency visits, surgical procedures, and hospitalizations as well as loss of productivity in the 4 weeks preceding enrollment.

Results. Enrollment was 141 patients, 79 with LN and 62 LNN. Patients with LN were more likely to visit rheumatologists and nephrologists, undergo diagnostic tests, and had higher costs for medications than patients who were LNN. The annual healthcare cost averaged $CAN 12,597 ± 9946 for patients with LN and $10,585 ± 13,149 for patients who were LNN, a difference of $2012 (95% CI –$2075, $6100). Patients with ALN had more diagnostic tests and surgical procedures, contributing to a significantly higher annual direct cost ($14,224 ± 10,265) compared to patients with ILN ($9142 ± 8419) and a difference of $5082 (95% CI $591, $9573). The healthcare cost was not different between patients with ALNN and patients with ILNN. In patients with LN and patients who were LNN, < 50% were employed and on average missed 6.5–9 days of work per month. The loss of productivity was significantly higher for caregivers of patients with LN than caregivers of patients who were LNN.

Conclusion. Healthcare cost and loss of productivity were similar between patients with LN and patients who were LNN; the loss of productivity for caregivers is higher for patients with LN; and the healthcare cost is greater in ALN than in ILN. (First Release Dec 15 2010; J Rheumatol 2011;38:658–66; doi:10.3899/jrheum.100482)

Key Indexing Terms:
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The worldwide incidence of systemic lupus erythematosus (SLE) is conservatively estimated at 12–104 cases per 100,000 individuals, with a 10:1 bias toward women[1,2,3,4]. In Canada, Bernatsky, *et al*[5] estimated the prevalence rate of SLE at 51 cases per 100,000 individuals, with a 7:1 to 10:1 bias toward women depending on different age categories. SLE has an unpredictable course, with flares and remissions of varying duration. The best characterized organ pathology is in the kidney, in which renal biopsies display mesangial cell proliferation, inflammation, necrosis, basement membrane abnormalities, and immune complex deposition[6,7]. An estimated 25% to 60% of patients with SLE develop renal involvement over time and may require expensive treatments and procedures including pharmacotherapy, biopsies, dialysis, and transplants[8,9,10].

The economic effect of SLE is substantial. A 1993 Canadian study[11] used self-reported data to quantify total direct and indirect costs for patients with SLE in 2 consecutive years. The mean total annual cost was $13,094 in the first year and $14,834 in the second year. Resource utilization was higher in the patients with SLE compared to the general population for both hospitalizations and physician visits. About half of the reported costs were indirect. Medical care costs for patients with SLE in the United States tend to be higher, although this was not associated with better medical outcomes[12,13,14,15].

Functional impairment is common, with higher levels of depression, fatigue, pain, and cognitive difficulties reported by patients with SLE compared with healthy controls[16]. Work disability is also a frequent consequence of having SLE, with one study finding 40% of patients no longer employed an average of 3.4 years after SLE diagnosis[17]. A Canadian study[18] found that within the first year of diagnosis, only 47% of patients were employed and overall 23% of patients were on work disability. Another Canadian study in SLE[19] reported an employment rate of 49.8%, and 19% of the patients were on work disability. Because SLE affects people, particularly women, in their prime working years[17,20], those with the disease are often unable to work in the period of life typically associated with the highest earnings. Even if an employee continues working, flares of the disease can lead to missed workdays and disability, affecting productivity.

We performed a cross-sectional cost-of-illness study from 2004 to 2009 in tertiary rheumatology specialty centers in Canada on patients with SLE, with and without lupus nephritis. The study identified the direct medical cost as well as loss of productivity for both patients and their caregivers.

MATERIALS AND METHODS

Patients for our study were selected from those attending 5 tertiary specialty clinics across Canada (2 centers in Toronto, 1 in Montreal, 1 in London, and 1 in Winnipeg). All centers are major referral centers accepting patients with SLE from family physicians and other medical specialties in the community and other hospitals. Patients attending these centers were approached to participate in the Lupus Nephritis New Emerging Team (LuNNET) study, which for 5 years followed patients with SLE who have active and inactive disease and those with and without lupus nephritis. All patients had to meet at least 4 out of 11 criteria for SLE established by the American College of Rheumatology (ACR)[21], but patients with endstage renal disease, on dialysis, and/or with transplantation were not eligible for our study. Therefore, the study patients were representative of those attending the outpatient clinics of these tertiary specialty clinics. Analyses were restricted to the baseline data.

All patients gave their informed consent and the protocol was approved by the Research Ethics Board of each participating center.

Patients were classified into 2 groups: (1) those with lupus nephritis (LN) defined by histological findings on renal biopsies or by laboratory abnormalities in the absence of renal biopsy, defined as proteinuria > 0.5 g/24 hours and/or presence of urinary cellular casts ever; and (2) those without lupus nephritis (lupus nephritis-negative, LNN), who had no renal abnormalities. These 2 groups were further subclassified into those with active (ALN, ALNN) and inactive (ILN, ILNN) disease. Disease activity was determined using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K). SLEDAI > 6 was considered an active disease[22,23].

Patients were asked to respond to a demographic questionnaire about age, sex, education level, ethnicity, age at diagnosis, and SLE disease duration.

Conventional health services use was evaluated using a portion of a validated questionnaire[24]. It inquires about the use of all health services over the preceding 4 weeks without asking the respondents to make attributions to SLE or other medical conditions. Patients reported on outpatient use of physicians and other healthcare professionals, laboratory tests, imaging procedures, renal dialysis, prescription and nonprescription medications, assistive devices, emergency room visits, ambulance use, and outpatient surgery as well as stays in acute and nonacute care institutions. These data were used to generate medical costs from methods used for economic analyses in various rheumatic diseases[11,12,25,26,27].

We calculated average annualized direct medical cost estimates by multiplying health service use levels by the appropriate unit prices. All costs are Canadian dollars unless otherwise specified. Prices were determined from a variety of sources, as documented[28]. For physician services and healthcare professionals as well as technical components of investigative tests (e.g., laboratory, imaging, etc.), we estimated Canadian unit prices as an average between government reimbursement fee schedules in the 2 provinces (Quebec and Ontario) that account for the largest part of health expenditures in Canada[29]. Laboratory cost estimates also relied on additional information from private clinic outpatient laboratories. For the services of allied healthcare workers (physiotherapists, social workers, etc.), we obtained salary estimates from the relevant professional associations. Pricing of assistive devices was performed using information from provincial insurance programs or suppliers.

The cost of hospitalization (both acute care hospitals and the complex continuing care) in all facilities was estimated using the Resource Intensity Weight method[30,31,32]. This method assigns weights based on the admission case mix group and using data provided by the Institute of Health Economics and Ontario Case-Costing project[33]. The estimated cost per chronic care day is $417.

Patients were also asked to report on hospital emergency visits, ambulance use, day procedures, and medical day/night care services. An average cost of $173 per emergency room visit was used in our study as reported by the Ministry of Health and Long-term Care in Ontario in 2004, Statistics Canada[34], the Institute of Health Economics, and other sources[35].

The costs of ambulatory visits (i.e., biopsy procedures) were estimated

by multiplying the assigned Day Procedure Group Resource Intensity Weight[30,31,32] for each visit by the provincial average cost per weighted case. Estimates of prescription and nonprescription medication costs were calculated as the product of the weighted average cost per milligram, total daily dose, and therapy duration, with cost data obtained from the Ontario Drug Benefit Plan fees for medications, and adding a retail markup of 8%.

Productivity losses due to disease arise from inabilities to perform work both in the labor market (paid labor) and in unpaid work (e.g., housework). Lost productivity in our sample was determined from self-reported data regarding the days that patients were unable to work, the time they spent seeking healthcare, and the time loss incurred by family and other unpaid caregivers.

Statistical analysis was performed using SPSS, version 16 (SPSS, Chicago, IL, USA) to provide descriptive summary statistics and frequency distributions. Unpaired Student t-test or chi-squared test was used for group comparisons. Mean differences between groups and 95% CI for the mean differences were calculated.

RESULTS

Subject demographics. Subjects for our study included 141 patients with SLE from 5 centers across Canada. Subjects had a mean (SD) age of 39.7 (14.1) years; 95.8% were women, the majority were white (48.2%), followed by Asians (23.4%); and 76.6% had at least completed high school, including those that had some postsecondary education.

Subjects had mean (SD) ACR criteria for SLE of 6.4 (1.7), diagnosis age of 28.1 (13.3) years, SLE duration of 11.5 (9.9) years, and SLEDAI-2K score (out of maximum score of 105) of 7.6 (6.2). A total of 56% (n = 79) met the criteria for LN. Among patients with SLE who had LN, 53 had active and 26 had inactive disease. Among patients with LNN (n = 62, 44%), 38 had active and 24 had inactive disease.

Healthcare resource utilization and costs: comparison between LN and LNN. Patients with LN were significantly younger (36.5 ± 13.6 vs 43.8 ± 15.1 years; mean difference –7.26; 95% CI –12.1, –2.4) and had a higher SLEDAI score (9.5 ± 7.0 vs 5.1 ± 3.8; mean difference 4.3; 95% CI 2.5, 6.2) compared to patients who were LNN. SLE disease duration (10.9 ± 9.7 vs 12.3 ± 10.3 years; mean difference –1.4; 95% CI –4.8, 2.1) was similar between the 2 groups.

Healthcare costs and resource use based on patients' self-report in the preceding 4 weeks were compared between patients with LN and patients who were LNN and are reported in Table 1. Although there was no significant difference in the combined number of visits to medical doctors and allied health professionals between LN and LNN groups, there were some differences in the number of visits to medical subspecialists. The LN group had a trend toward a higher number of visits to all physicians and to rheumatologists and a significantly higher number of visits to their family physicians and nephrologists. This trend was associated with a higher healthcare cost. On the other hand, patients in the LNN group had more visits to internists and other physician specialists excluding nephrologists, rheumatologists, family physicians, and dermatologists. The total number of visits to non-physician health professionals was similar between patients with LN and patients who were LNN.

The total number of diagnostic tests [blood, urine, radiograph, computed tomography scan, magnetic resonance imaging (MRI), and other tests including endoscopies, ultrasound imaging, biopsy procedure, breathing test, Pap smear, visual test, Doppler test, Holter monitor, cytoscopy, bone density, mammogram, and electrocardiogram] taken by patients with LN was significantly higher than that of patients who were LNN, although this was not associated with a significantly higher cost in patients with LN when all diagnostic tests were combined. The higher number of diagnostic tests in patients with LN was mostly driven by a significantly higher number of blood and urine tests ordered for these patients; however, patients with LNN had higher numbers of other tests such as endoscopy, MRI, and ultrasound.

The use of alternative treatments such as acupuncture, massage therapy, homeopathy, relaxation, and meditation, and the use of megadose vitamins, minerals, glucosamine, and herbal medicines as well as special diet programs was similar between patients with LN and patients who were LNN. As well, the use of assistive devices such as crutches, canes, walkers, braces, wheelchairs, bath rails, special toilet seats, special shower seats, hospital beds, and orthopedic footwear was not different between the 2 groups. There was a trend toward a higher number of hospital emergency visits and surgical procedures in patients with LN compared to patients who were LNN. The cost of both prescription and nonprescription medications was also significantly higher in patients with LN compared to those with LNN. The annual healthcare cost (calculated by multiplying the 4-week cost by 13) was slightly higher for patients with LN compared to patients who were LNN; however, this difference was not statistically significant.

Comparison between active and inactive LN. Demographic characteristics of patients with ALN, ILN, ALNN, and ILNN are presented in Table 2.

Among patients with LN, 53 had active disease (ALN) and 26 had inactive disease (ILN) at the time of enrollment. Age was similar between the 2 groups (35.2 ± 12.4 vs 39.2 ± 15.7 years, respectively; mean difference –4.0; 95% CI –10.5, 2.5). Patients with ALN had a significantly higher SLEDAI score (12.1 ± 6.6 vs 4.3 ± 4.3; mean difference 7.9; 95% CI 5.4, 10.4) and shorter SLE disease duration (8.0 ± 7.3 vs 16.7 ± 11.3 years; mean difference –8.6; 95% CI –13.6, –3.7) compared to patients with ILN.

Healthcare resource use and costs, comparing patients with active LN and inactive disease, are reported in Table 3. Compared to patients with ILN, those with ALN had a significantly higher number of visits to medical doctors, more specifically rheumatologists and nephrologists. Patients with ALN also had a significantly higher number of surgical procedures and diagnostic tests such as blood tests, urine

Table 1. Resource use and healthcare costs for patients with SLE with and without lupus nephritis. Results are reported as mean (SD) or percentage. Comparisons between the 2 groups were done using unpaired Student t test or chi-squared test. $p < 0.05$ is considered a statistically significant difference when applicable.

No. Visits/Use	Resource Use LN, n = 79	Resource Use LNN, n = 62	Cost Can$/4 Weeks LN	Cost Can$/4 Weeks LNN	Cost Can$/4 Weeks Mean (95% CI)
Health professional (MD[1] + non-MD[2])	3.0 (2.9)	2.5 (3.1)	139 (118)	123 (160)	17 (–30, 63)
Rheumatologist	0.8 (0.7)	0.6 (0.8)	50 (44)	35 (47)	14 (–1, 30)
Nephrologist	0.3 (0.7)	0.0 (0.0)	19 (42)*	0 (0)	19* (9, 30)
Family physician	0.9 (1.3)	0.5 (0.9)	27 (41)*	15 (27)	12* (0.5, 23)
Internist	0.01 (0.1)	0.1 (0.3)	1 (7)*	7 (20)	–6* (–12, –1)
Dermatologist	0.05 (0.2)	0.03 (0.2)	2 (9)	1 (7)	1 (–2, 3)
Ophthalmologist	0.1 (0.4)	0.2 (0.4)	6 (15)	7 (17)	–2 (–7, 4)
Other MD specialties	0.1 (0.5)	0.5 (0.9)	5 (17)*	18 (29)	–13* (–21, –5)
Total MD visits	2.4 (2.2)	1.9 (1.8)	112 (96)	86 (83)	26 (–4, 55)
Total non-MD visits	0.6 (1.7)	0.6 (2.2)	28 (67)	35 (111)	–7 (–39, 25)
Diagnostic tests	3.5 (3.5)	2.3 (3.1)	147 (277)	148 (301)	–1 (–97, 96)
Blood	1.7 (1.7)	1.1 (1.5)	31 (32)*	20 (28)	11* (1, 21)
Urine	1.2 (1.5)	0.5 (0.9)	14 (17)*	5 (10)	8* (4, 13)
Radiographs	0.2 (0.6)	0.2 (0.4)	8 (24)	6 (15)	2 (–5, 9)
CT scan	0.1 (0.4)	0.1 (0.2)	35 (144)	25 (97)	9 (–31, 50)
MRI	0.0 (0.0)	0.03 (0.2)	0 (0)	23 (125)	–23 (–51, 5)
Other tests[3]	0.3 (0.6)	0.5 (1.1)	59 (199)	68 (199)	–9 (–75, 58)
Alternative treatments	0.9 (1.3)	0.8 (1.5)	83 (192)	92 (197)	–9 (–75, 56)
Assistive devices	0.3 (0.8)	0.2 (0.5)	34 (121)	54 (195)	–21 (–74, 33)
Hospital emergency, %	14.1	8.1	24 (61)	14 (48)	10 (–8, 29)
Surgical procedures, %	6.4	1.6	51 (198)	13 (102)	38 (–13, 90)
Hospitalization, %	6.5	5.0	76 (330)	118 (595)	–42 (–212, 128)
Length of hospital stay, days	2.8 (1.6)	5.7 (3.8)			
Medications, %	99	100	398 (383)*	229 (287)	169* (54, 285)
Total cost, $			969 (765)	814 (1011)	155 (–149, 458)
Annual cost, $			12,597 (9946)	10,585 (13,149)	2012 (–2075, 6100)

* Statistically significant from LNN at $p < 0.05$. [1] Rheumatologist, nephrologists, internist, family physician, gynecologist, ophthalmologist, dermatologist, immunologist, respirologist, cardiologist, gastroenterologist, orthopedic surgeon, plastic surgeon, bariatric surgeon, endocrinologist, dentist, neurologist, psychiatrist, and ear-nose-throat specialist. [2] Naturopath, dietician, pharmacist, acupuncturist, psychotherapist, nurse, massage therapist, physiotherapist, and chiropractor. [3] Endoscopy, ultrasound imaging, biopsy procedure, breathing test, Pap smear, visual fields test, Doppler test, Holter monitor, cytoscopy, bone mineral density, mammogram, and electrocardiogram. SLE: systemic lupus erythematosus; LN: lupus nephritis; LNN: lupus nephritis-negative; CT: computed tomography; MRI: magnetic resonance imaging.

Table 2. Demographic characteristics of patients with active and inactive disease.

Characteristic	Active LN, n = 53	Inactive LN, n = 26	Active LNN, n = 38	Inactive LNN, n = 24
Age, yrs (SD)	35.2 (12.4)	39.2 (15.7)	43.2 (16.2)	44.8 (13.4)
Women, %	79.2	88.5	92.1	87.5
White, %	36.5	50.0	60.5	54.2
Employed, %	51.0	42.3	47.4	41.4
SLE duration, yrs (SD)	8.0 (7.3)	16.7 (11.3)	11.4 (10.7)	13.7 (9.8)
SLEDAI-2K score (SD)	12.1 (6.6)	4.3 (4.3)	6.8 (3.6)	2.5 (2.1)

LN: lupus nephritis; LNN: lupus nephritis-negative; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index-2000.

tests, and radiographs performed compared to ILN. The total annual medical cost was significantly higher in patients with ALN compared to patients with ILN, with a difference in total cost of $5082 (95% CI $591, $9573).

Comparison between active and inactive LNN. Among patients who were LNN, 38 had active disease (ALNN) and 24 had inactive disease (ILNN) at the time of enrollment. Age (43.2 ± 16.2 vs 44.8 ± 13.4 years, respectively; mean difference –1.7; 95% CI –9.3, 5.9) and SLE duration (11.4 ± 10.7 vs 13.7 ± 9.8 years; mean difference –2.4; 95% CI –7.8,

Table 3. Healthcare resource use and cost in patients with active and inactive lupus nephritis. Results are reported as mean (SD) or percentage. Comparisons between the 2 groups were done using unpaired Student t test or chi-squared test. $p < 0.05$ is considered statistically significant difference where applicable.

No. Visits/Use	Resource Use ALN, n = 53	Resource Use ILN, n = 26	Cost Can$/4 Weeks ALN	Cost Can$/4 Weeks ILN	Cost Can$/4 Weeks Mean (95% CI)
Health professional					
(MD[1] + non-MD[2])	3.3 (3.0)	2.5 (2.6)	152 (122)	114 (109)	37 (–17, 92)
Rheumatologist	0.9 (0.8)	0.5 (0.6)	57 (46)*	34 (36)	23* (4, 42)
Nephrologist	0.5 (0.9)	0.0 (0.0)	29 (49)*	0 (0)	29* (10, 48)
Family physician	1.0 (1.5)	0.7 (0.8)	31 (46)	20 (26)	11 (–6, 27)
Internist	0.02 (0.1)	0.0 (0.0)	1 (9)	0 (0)	1 (–1, 4)
Dermatologist	0.06 (0.2)	0.04 (0.2)	2 (9)	1 (8)	1 (–3, 5)
Ophthalmologist	0.1 (0.4)	0.2 (0.4)	5 (15)	7 (16)	–1 (–9, 6)
Other MD specialties	0.2 (0.5)	0.04 (0.2)	6 (19)	2 (13)	4 (–4, 11)
Total MD visits	2.8 (2.5)	1.5 (1.3)	132 (101)	71 (71)	61* (17, 105)
Total non-MD visits	0.4 (1.4)	1.0 (2.1)	20 (59)	43 (80)	–23 (–59, 13)
Diagnostic tests	4.3 (3.8)	1.8 (2.0)	193 (325)*	53 (83)	140* (46, 235)
Blood	2.0 (1.8)	1.0 (1.2)	37 (34)*	19 (22)	18* (6, 31)
Urine	1.5 (1.7)	0.5 (0.8)	17 (19)	6 (9)	11 (5, 18)
Radiographs	0.3 (0.7)	0.1 (0.4)	11 (28)	3 (13)	8 (–1, 17)
CT scan	0.1 (0.4)	0.04 (0.2)	45 (167)	15 (77)	29 (–25, 84)
MRI	0.0 (0.0)	0.0 (0.0)	0 (0)	0 (0)	0 (0, 0)
Other tests[3]	0.4 (0.7)	0.2 (0.4)	84 (240)*	10 (27)	74* (7, 140)
Alternative treatments	0.8 (1.3)	0.9 (1.5)	90 (205)	68 (164)	21 (–66, 109)
Assistive devices	0.2 (0.6	0.4 (1.1)	29 (104)	43 (151)	–14 (–81, 52)
Hospital emergency, %	17.3	7.7	30 (66)	13 (47)	17 (–9, 43)
Surgical procedures, %	9.6	0.0	77 (239)*	0.0	77* (11, 144)
Hospitalization, %	7.8	3.8			
Length of hospital stay, days	2.5 (1.7)	4.0 (0.0)	82 (334)	64 (327)	18 (–142, 177)
Medications, %	100	96	433 (386)	327 (375)	106 (76, 287)
Total cost, $			1094 (790)*	703 (648)	391* (45, 736)
Annual cost, $			14,224 (10,265)*	9142 (8419)	5082* (591, 9573)

* Statistically significant from ILN at $p < 0.05$. [1] Rheumatologist, nephrologist, internist, family physician, gynecologist, ophthalmologist, dermatologist, immunologist, respirologist, cardiologist, gastroenterologist, orthopedic surgeon, plastic surgeon, bariatric surgeon, endocrinologist, dentist, neurologist, psychiatrist, and ear-nose-throat specialist. [2] Naturopath, dietician, pharmacist, acupuncturist, psychotherapist, nurse, massage therapist, physiotherapist, and chiropractor. [3] Endoscopy, ultrasound imaging, biopsy procedure, breathing test, Pap smear, visual fields test, Doppler test, Holter monitor, cytoscopy, bone mineral density, mammogram, and electrocardiogram. ALN: active lupus nephritis; ILN: inactive lupus nephritis; CT: computed tomography; MRI: magnetic resonance imaging.

3.0) were similar between the 2 groups and the SLEDAI score was significantly higher in the ALNN group compared to the ILNN group (6.8 ± 3.6 vs 2.5 ± 2.1; mean difference 4.4; 95% CI 2.8, 5.9).

There was no significant difference between patients with active and inactive LNN with respect to the number of visits to healthcare professionals and total number of diagnostic tests performed; however, the number of urine tests was significantly higher in patients with active disease compared to those with inactive disease (Table 4). There were no differences for the use of assistive devices, alternative treatments, hospital emergency visits, surgical procedures, hospitalization, and length of hospital stay between the active and inactive patients with LNN. There was a trend toward a higher total healthcare cost in ALNN compared to ILNN, although this difference did not reach statistical significance (Table 4).

Loss of productivity. Loss of productivity for both patients and their caregivers is reported in Table 5. In LN and LNN patient groups, less than 50% of patients were employed. Among those employed, on average both patients with LN and patients who were LNN worked 4.5 days per week and 8 hours per day. They missed on average 4.1–8.5 days of work per month due to illness, and patients with LN were more likely to miss work than patients who were LNN. The percentage of patients who required help from others (26%–36%) was not different between LN and LNN. However, the number of hours others missed work to assist the patients was significantly higher for patients with LN compared to patients who were LNN, with a difference of 6.7 hours (95% CI 2.7, 10.8; Table 5).

DISCUSSION

Our study demonstrated that healthcare cost and resource use is substantial in patients with SLE regardless of renal involvement. The annual healthcare cost was increased when patients experienced flares and higher disease activity, as this required more visits to healthcare professionals

Table 4. Resource use and healthcare costs in patients with active and inactive SLE without lupus nephritis. Results are reported as mean (SD) or percentage. Comparisons between the 2 groups were done using unpaired Student t test or chi-squared test. $p < 0.05$ is considered a statistically significant difference when applicable.

No. Visits/Use	Resource Use ALNN, n = 38	Resource Use ILNN, n = 24	Cost Can$/4 Weeks ALNN	Cost Can$/4 Weeks ILNN	Cost Can$/4 Weeks Mean (95% CI)
Health professional (MD[1] + non-MD[2])	2.2 (2.2)	2.6 (4.2)	126 (132)	117 (200)	8 (–76, 93)
Rheumatologist	0.7 (0.9)	0.4 (0.7)	43 (49)	23 (41)	20 (–3, 43)
Nephrologist	0.0 (0.0)	0.0 (0.0)	0 (0)	0 (0)	0 (0, 0)
Family physician	0.6 (1.0)	0.4 (0.6)	18 (31)	12 (20)	6 (–7, 19)
Internist	0.2 (0.4)	0.04 (0.2)	10 (24)	3 (13)	7 (–2, 17)
Dermatologist	0.0 (0.0)	0.1 (0.3)	0 (0)	3 (11)	–3 (–8, 1)
Ophthalmologist	0.2 (0.5)	0.2 (0.4)	7 (18)	7 (16)	0.3 (–8, 9)
Other MD specialties	0.4 (0.8)	0.4 (0.6)	15 (28)	21 (31)	–6 (–22, 9)
Total MD visits	2.1 (2.0)	1.5 (1.6)	98 (87)	67 (74)	32 (–10, 73)
Total non-MD visits	0.3 (1.1)	1.1 (3.2)	25 (81)	51 (146)	–26 (–92, 41)
Diagnostic tests	2.6 (3.3)	1.7 (2.7)	167 (358)	117 (181)	49 (–89, 187)
Blood	1.2 (1.3)	0.9 (1.7)	23 (25)	16 (32)	6 (–8, 21)
Urine	0.7 (1.0)	0.2 (0.4)	7 (12)*	2 (4)	6* (1, 10)
Radiograph	0.1 (0.3)	0.2 (0.4)	4 (11)	8 (19)	–4 (–13, 5)
CT scan	0.0 (0.0)	0.2 (0.4)	0 (0)*	66 (150)	–66* (–114, –17)
MRI	0.05 (0.2)	0.0 (0.0)	37 (159)	0 (0)	37 (–15, 89)
Other tests[3]	0.6 (1.3)	0.3 (0.7)	95 (247)	25 (60)	70 (–14, 154)
Alternative treatments	0.8 (1.5)	0.9 (1.6)	97 (209)	85 (182)	12 (–89, 113)
Assistive devices	0.2 (0.6)	0.1 (0.3)	54 (209)	54 (175)	0.2 (–99, 99)
Hospital emergency, %	10.5	4.2	18 (54)	7 (35)	11 (–12, 34)
Surgical procedures, %	2.6	0.0	21 (130)	0.0	21 (–22, 64)
Hospitalization, %	8.3	0.0			
Length of hospital stay, days	5.7 (3.8)	0.0	197 (762)	0.0	197 (–61, 455)
Medications, %	100	100	247 (326)	200 (214)	47 (–90, 184)
Total cost, $			974 (1191)	581 (621)	393 (–84, 871)
Annual cost, $			12,666 (15,489)	7,551 (8075)	5116 (–1088, 11,318)

* Statistically significant from ILNN at $p < 0.05$. [1] Rheumatologist, nephrologist, internist, family physician, gynecologist, ophthalmologist, dermatologist, immunologist, respirologist, cardiologist, gastroenterologist, orthopedic surgeon, plastic surgeon, bariatric surgeon, endocrinologist, dentist, neurologist, psychiatrist, and ear-nose-throat specialist. [2] Naturopath, dietician, pharmacist, acupuncturist, psychotherapist, nurse, massage therapist, physiotherapist, and chiropractor. [3] Endoscopy, ultrasound imaging, biopsy procedure, breathing test, Pap smear, visual fields test, Doppler test, Holter monitor, cytoscopy, bone mineral density, mammogram, and electrocardiogram. ALNN: active lupus nephritis-negative; ILNN: inactive lupus nephritis-negative; CT: computed tomography; MRI: magnetic resonance imaging.

Table 5. Loss of productivity of patients with and without lupus nephritis and their caregivers. Results are reported as mean (SD) or percentage. Comparisons between the 2 groups were done using unpaired Student t test or chi-squared test.

Productivity Measures	LN	LNN	Mean (95% CI)
Employed, %	48.1	45.2	
Of those employed, no. hours per day worked in the last 6 months	8.1 (3.1)	8.5 (1.7)	–0.4 (–1.6, 0.9)
Of those employed, no. days/week worked in the past 6 months	4.5 (1.5)	4.6 (1.1)	–0.1 (–0.7, 0.5)
Of those employed, percentage of patients who missed work	56.8	42.9	
Of those employed, no. days of missed work in the past month	8.5 (9.5)	4.1 (7.0)	4.4 (–1.2, 5.7)
Patients requiring help from others for doctor/hospital visits, %	36.4	25.8	
No. hours of help from others in the past month	12.8 (18.4)	31.5 (68.4)	–19.3 (–56.2, 17.6)
No. hours others missed work to assist in the past month	8.5 (9.2)*	1.73 (3.5)	6.7* (2.7, 10.8)

* Statistically significant from LNN at $p < 0.05$. LN: lupus nephritis; LNN: lupus non-nephritis.

and more diagnostic tests. The loss of productivity was also significant for both patients and their caregivers, as less than 50% of the patients in our study were employed despite an average age < 40 years and high prevalence of postsecondary education in this cohort.

SLE is an autoimmune disease affecting mostly young women. In Canada, 1 in 1000 young women have SLE[5]. The 10-year survival rate is improving (85% at 10 years), but the prevalence is increasing[36]. SLE has an unpredictable course, with flares and remissions of varying duration, but under-

lying the reversible inflammatory changes is irreversible organ damage caused by the disease itself and possibly by some of its treatments. The best-characterized organ pathology and abnormalities are reported for the kidney[6,7], with the prevalence rate of 25% to 60% of patients with SLE. This pathology may require expensive treatments and procedures[8,9,10]. Other organ systems affected usually display nonspecific inflammation or vascular abnormalities. Persons with SLE also have a 5- to 9-fold increased risk for cardiovascular disease (CVD) compared to the Framingham cohort and after adjusting for traditional risk factors[37,38,39,40,41]. The prevalence of CVD in SLE is estimated at 6%–15% and the annual incidence at 1.5%[38,40,42]. The management of CVD risk factors and its associated complications often requires more frequent clinic visits, more diagnostic tests, emergency visits, and hospitalization, needs that can result in a significant loss of productivity for both patients and their caregivers. The peak occurrence of CVD in SLE is observed 7–10 years after diagnosis in women in their late 30s and early 40s. Neuropsychiatric conditions are also commonly seen in SLE and are associated with an increased healthcare cost[43].

In our study, the annual direct medical cost was estimated at $12,597 for patients with renal involvement and $10,585 for patients without renal involvement. The cost increased for patients with LN who had an active disease at the time of enrollment to an average annual medical cost of $14,224, and we estimated the $5082 additional cost attributable to having ALN. Unlike other studies[44,45], the difference in the direct medical cost was not significantly different between patients with SLE and without nephritis. However, we observed a trend in the LN group toward a higher number of visits to physicians including rheumatologists, with a significantly higher number of visits to nephrologists. The LNN group had more visits to other medical specialists. In addition, the monthly cost of medications was significantly higher for patients with LN compared to those who were LNN. In Canada, the cost of medications is not part of the universal health coverage and is covered by different providers. Most employed persons will have their medication cost covered by private complementary insurance. In the absence of private medication insurance, coverage includes self-payment or relying on government-sponsored programs with a copayment that is proportional to the patient's financial situation. Since half of our SLE population is employed, patients with SLE with nephritis are at a greater disadvantage since they use more drugs and therefore pay more for medications when they have no or restricted drug coverage. This could have an effect on drugs used and adherence to treatment.

The estimated direct medical cost in our study was in line with previous estimates for patients with SLE[11,12,13,44,46] in Canada, the United Kingdom, and the United States that involved data on healthcare resource use based on patients' self-reports. In one study[44], the 4 years of cumulative medical costs based on renal damage assessed by the Systemic Lupus International Collaborating Clinics damage index of 0, 1, 2, and 3 were $20,337, $27,869, $51,191, and $99,544, respectively. Each unit-increase in renal damage was associated with a 24% increase in direct medical costs. However, our estimate was lower than that obtained by Carls, *et al*[45], in which patients were selected from a database that contained de-identified, standardized medical and pharmaceutical claims data for about 17 million enrollees annually, from over 100 large employers in the United States. Carls, *et al*[45] reported an annual medical expenditure of US$19,502, which was more than twice that of controls. The difference in mean total medical expenditures for patients with SLE without nephritis compared to controls was US$8628, while the difference for patients with SLE with nephritis compared to controls was surprisingly high at US$46,862. The costs for inpatient admission and outpatient clinic visits were the major contributing factors in the higher healthcare cost for patients with nephritis, accounting for about US$53,000. Although we cannot explain such a big difference in cost estimates between the 2 studies, one explanation could be that Carls's study included more patients whose disease was newly diagnosed and/or active as well as patients with advanced renal failure and on dialysis, while we enrolled patients with both active and inactive disease of various disease duration but rarely at the onset of their disease, and excluded those with endstage renal disease or on dialysis. The diagnosis of LN in Carls's study was based on the presence of any medical claim with a diagnosis or procedure code consistent with nephritis occurring in the 12 months of analyses. This could have resulted in inclusion of more diagnostic procedures and in patient admissions. Cost differences could also be attributed to differences in the healthcare systems and data collection and costing methodologies.

Carls, *et al*[45] also compared the average annual per-patient cost burden of SLE to 10 other chronic conditions: asthma, hypertension, diabetes, chronic obstructive pulmonary disease, bipolar disorder, heart disease, rheumatoid arthritis, ulcerative colitis, Crohn's disease, and renal failure. Of the 10 conditions examined, only Crohn's disease and renal failure had higher average annual per-patient costs, and the difference between SLE and Crohn's disease costs was quite small. Patients with SLE and nephritis had the highest total costs (direct and indirect): US$28,508 greater than the next highest disease category (renal failure).

Regression results showed that greater disease activity, longer disease duration, and worse physical and mental health were significant predictors of higher direct costs in one study[46].

The loss of productivity due to SLE was also extensive in our study, because < 50% of the patients were employed. About one-third of the patients needed assistance from

others and that was associated with loss of productivity for the caregivers. This loss of productivity was significantly higher for caregivers of patients with nephritis compared to those without nephritis. This finding is in agreement with Panopalis, *et al*[46], in which the annual cost of lost productivity was US$8659 and was significantly higher than the US national average. Panopalis, *et al*[46] reported that 76.8% of patients with SLE were employed at the time of diagnosis and that was comparable with the US national average employment rate of 75.3%. However, after an average SLE duration of 13 years, employment status dropped to 48.7%, with a drop from an average of 30.8 hours of work per week to 19.1 hours. Other Canadian studies have also reported an employment rate < 50% among patients with SLE[18,19], and 19%–23% of patients were on work disability. Older age, greater disease activity, longer disease duration, less education, and worse physical and mental health status were shown to be significant predictors of higher cost because of changes in work productivity in various studies[18,19,46,47,48].

Our study had some limitations. The subjects were selected from 5 university-affiliated academic hospitals across Canada with significant SLE research activity. This may have resulted in more frequent visits to the clinics and a larger number of diagnostic tests performed and thus inflation of the healthcare cost. On the other hand, patients with SLE who have more severe disease such as endstage renal disease or who are on dialysis as well as those who were admitted to an intensive care unit and required more diagnostic tests were less likely to participate in research studies, and thus the calculated annual healthcare cost in our study may be underestimated. By study design, we did not have any patients with severe disease such as endstage renal disease and/or on dialysis. Further, these data may not be generalizable to patients with SLE in rural areas who have limited access to healthcare and specialty clinics. They may have less frequent visits to healthcare professionals/specialized physicians and have fewer diagnostic tests, but the loss of productivity may be more substantial for both patients and their family members if they need to travel or need to take time off work to see a healthcare professional or to perform diagnostic tests.

Another limitation of our study was that patients with LN tended to be younger than patients without nephritis. This may be one reason why we observed a small cost difference between patients with and those without nephritis, and the occurrence of nephritis may have been confounded with age. Also, the same unit costs were applied to patients with different disease severity, age, and sex, and perhaps people with more severe disease and those who are older may require more expensive treatments. However, we applied unit costs for each different test and physician visit; physician and laboratory costs should really not vary with disease characteristics and presumably the need to adjust costs by disease and patient characteristics applies primarily to hospital stays. Since there was little difference between physician and test costs among the nephritis and non-nephritis and inactive and active patients, there is also likely to be little difference between hospital costs even if adjusted by disease severity. Further, the survey instrument used for our study may not have had sufficient precision to identify differences between patients with and those without nephritis and active and inactive SLE for various reasons. The survey does not specifically inquire whether the use of any of the services was because of active/inactive SLE disease or nephritis or non-nephritis. It inquires only about visits to different healthcare specialists and the types of diagnostic tests performed, and the causes for hospitalization and emergency visits were not queried. In addition, the report on healthcare resource utilization and loss of productivity was based on patients' self-report in the 4 weeks prior to enrollment, which is subject to recall bias. Also, assuming that the 4-week study period is representative of the entire year may overestimate the costs for the less ill who see physicians infrequently. Perhaps data collected prospectively for a longer duration from these patients would give a more accurate estimate of the healthcare cost.

Patients with SLE, particularly those with active lupus nephritis, incur substantial healthcare costs and experience considerable productivity loss. Enhanced understanding of disease pathogenesis and improved management should lead to improved health, quality of life, and productivity and a commensurate decline in direct and indirect healthcare costs.

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