Clinical and Serologic Factors Associated with Lupus Pleuritis

SHIKHA MITTOO, ALLAN C. GELBER, CAROL A. HITCHON, EARL D. SILVERMAN, JANET E. POPE, PAUL R. FORTIN, CHRISTIAN PINEAU, C. DOUGLAS SMITH, HECTOR ARBILLAGA, DAFNA D. GLADMAN, MURRAY B. UROWITZ, MICHEL ZUMMER, ANN E. CLARKE, SASHA BERNATSKY, MARIE HUDSON, LORI B. TUCKER, ROSS E. PETTY, Canadian Network for Improved Outcomes in Systemic Lupus Erythematosus (CaNIOS), and CHRISTINE A. PESCHKEN

ABSTRACT. ***Objective.*** Pleuritis is a common manifestation and independent predictor of mortality in systemic lupus erythematosus (SLE). We examined the prevalence of pleuritis and factors associated with pleuritis in a multicenter Canadian SLE cohort.

Methods. We studied consecutive adults satisfying the American College of Rheumatology (ACR) classification criteria for SLE who had a completed Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI) score, at least 1 evaluable extractable nuclear antigen assay, and either a SLE Disease Activity Index (SLEDAI) or a SLE Activity Measure score. Pleuritis was defined as having pleuritis by satisfying the ACR criteria or the SLEDAI. Factors related to pleuritis were examined using univariate and multivariate logistic regression.

Results. In our cohort of 876 patients, 91% were women, 65% Caucasian, mean age (± SD) was 46.8 ± 13.5 years, and disease duration at study entry was 12.1 ± 9.9 years; the prevalence of pleuritis was 34% (n = 296). Notably, greater disease duration ($p = 0.002$), higher SDI score ($p \leq 0.0001$), age at SLE diagnosis ($p = 0.009$), and anti-Sm ($p = 0.002$) and anti-RNP ($p = 0.002$) seropositivity were significantly associated with pleuritis. In multivariate analysis with adjustment for disease duration, age at diagnosis, and SDI score, concomitant seropositivity for RNP and Sm were related to a nearly 2-fold greater prevalence of pleuritis (OR 1.98, 95% CI 1.31–2.82).

Conclusion. Pleuritis occurred in one-third of this Canadian cohort. Concomitant Sm and RNP seropositivity, greater cumulative damage, longer disease duration, and younger age at SLE disease onset were related to a higher rate of SLE pleural disease. (J Rheumatol First Release Feb 1 2010; doi:10.3899/jrheum.090249)

Key Indexing Terms:
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Pleuritis is a common and prominent feature of systemic lupus erythematosus (SLE) and together with pericarditis constitutes one of the 11 classification criteria for SLE[1]. Pleuritis, along with other types of pulmonary disease manifestations, occurs in 30%–60% of patients, and significantly increases the risk of short-term mortality in SLE[2-6]. We investigated the prevalence and factors related to pleuritis in a large contemporary SLE cohort. Moreover, a characteristic feature of lupus is its exuberant autoantibody response in which antibodies are directed against a range of self-anti-

From the Department of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada.

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S. Mittoo, MD, MHS, Assistant Professor, Department of Medicine, University of Manitoba; A.C. Gelber, MD, MPH, PhD, Associate Professor of Medicine, Johns Hopkins University, Baltimore, Maryland, USA; C.A. Hitchon, MD, MSc, Assistant Professor, Department of Medicine, University of Manitoba; E.D. Silverman, MD, Professor of Medicine, Department of Pediatrics, University of Toronto, Toronto, Canada; J.E. Pope, MD, MPH, Associate Professor of Medicine, University of Western Ontario, London, Canada; P.R. Fortin, MD, MPH, Professor of Medicine, Department of Medicine, University of Toronto; C. Pineau, MD, Assistant Professor, Department of Medicine, McGill University, Montreal, Canada; C.D. Smith, MD, Associate Professor, Department of Medicine, University of Ottawa, Ottawa, Canada; H.O. Arbillaga, MD, Staff Physician, Chinook Regional Hospital, Lethbridge, Canada; D.D. Gladman, MD; M.B. Urowitz, MD, Professor of Medicine, Department of Medicine, University of Toronto; M. Zummer, MD, Assistant Professor, Department of Medicine, University of Montreal School of Medicine, Montreal, Canada; A.E. Clarke, MD, MSc, Associate Professor; S. Bernatsky, MD, PhD, Assistant Professor; M. Hudson, MD, Assistant Professor, Department of Medicine, McGill University, Montreal, Canada; L.B. Tucker, MD; R.E. Petty, MD, Department of Paediatrics, University of British Columbia, Vancouver, Canada; C.A. Peschken, MD, MSc, Assistant Professor, Departments of Medicine and Community Health Sciences, University of Manitoba, Winnipeg, Canada.

Address correspondence to Dr. Dr. S. Mittoo, University of Manitoba Arthritis Center, RR149 – 800 Sherbrook Street, Winnipeg, Manitoba R3A 1M4. E-mail: shikha.hopkins@gmail.com

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gens. These autoantibodies serve as important diagnostic features and prognostic markers of the disease process. For example, antibodies directed against double-stranded DNA (dsDNA) and against the Smith (Sm) antigen both correlate strongly with lupus nephritis[7-9]. As with renal disease manifestations, autoantibodies may also serve as markers of pulmonary involvement in lupus. Specifically, antiphospholipid antibodies (aPL) have been associated with alveolar hemorrhage, anti-Ro antibodies with pneumonitis and shrinking lung syndrome, and anti-ribonucleoprotein (RNP) with interstitial lung disease[10-15]. Notably, in a prospective study of 626 patients with lupus from the United States, the LUMINA cohort, anti-RNP antibody was associated with rapid progression of pulmonary damage[16].

A key principle in clinical evaluation of patients with incident and prevalent lupus is to identify those at risk to develop meaningful disease manifestations, including inflammation of the pleural surfaces, with the goal of preventing irreversible organ and tissue damage before they occur. In this multicenter prospective cohort, we set out to determine (1) the prevalence of pleuritis among a multiethnic Canadian SLE cohort; and (2) the clinical and serologic features [including antibodies to dsDNA, Sm, RNP, Ro, La, and aPL — either anticardiolipin (aCL) or lupus anticoagulant (LAC) antibodies] associated with SLE pleuritis.

MATERIALS AND METHODS

Study population. The 1000 Faces of Lupus Cohort (1000 Faces) is a prospective multicenter observational cohort of incident and prevalent cases of adult and pediatric SLE. Its purpose is to characterize ethnic differences in the clinical manifestations, disease course, and outcome of SLE across Canada. The study has been approved by the Ethics Review Board of each participating site. Patients were enrolled at 14 sites across Canada, including 10 adult and 4 pediatric rheumatology clinics. Only adult patients are included in the current analysis.

Patients were eligible if they were identified by the site investigator(s) as having a clinical diagnosis of SLE.

Study variables. At the baseline visit, all available medical records were reviewed by the site investigators; clinical data were abstracted and entered onto a comprehensive database form. Clinical manifestations of SLE, i.e., those satisfying the American College of Rheumatology (ACR) criteria and those included in the revised Systemic Lupus Activity Measure (SLAM-2) and the revised SLE Disease Activity Index (SLEDAI-2K), were recorded[1,17-19]. Disease activity was measured at baseline and annually using the SLAM-2 and the SLEDAI-2K validated lupus activity scales[17-19]. Next, we modified the ACR criteria (m-ACR) and SLEDAI-2K (m-SLEDAI-2K) by subtracting the number attributed to pulmonary involvement from the total score. In addition, at cohort entry, components of the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI) were abstracted from the medical record, and reviewed with the patients during the interview[20].

Detailed sociodemographic data were recorded at the first visit and updated yearly, including age and sex. Self-reported ethnicity was categorized based on the format used by Statistics Canada[21] and coded into the following categories: Aboriginal (First Nations, Métis, Inuit, other), Asian (east Asian, southeast Asian, south Asian, central Asian, north African, Arabian peninsula, eastern Middle East, northern Middle East, other Middle Eastern/Arab), Black (African, Caribbean, North American), and Caucasian (European, North American, Australian/New Zealand, French Canadian, Acadian). Age of SLE onset was calculated from date of birth until the date of physician diagnosis of lupus according to the ACR criteria. Disease duration at enrollment was defined as duration from the date of physician diagnosis until the date at first study visit. Patients were also questioned about smoking habits. Ever smokers were defined as having smoked regularly, at least one cigarette per day for ≥ 3 months over their lifetime; nonsmokers were those who did not smoke regularly for ≥ 3 months over their lifetime.

Autoantibodies were screened at the baseline visit and annually thereafter, including antinuclear antibody (ANA), anti-Ro, anti-La, anti-Sm, anti-RNP, anti-dsDNA, and aCL or LAC (aPL). ANA were measured using immunofluorescence; antibodies to dsDNA were measured by ELISA or Farr assay. Testing for extractable nuclear antigens (anti-Ro, anti-La, anti-Sm, and anti-RNP) was by ELISA followed by a confirmatory immunoblot; seropositivity was defined as one or more positive assays for that particular antibody.

Outcome measures. Pleuritis was defined as either serositis according to the ACR criteria, or physician-recorded pleuritis on the SLEDAI-2K index[1,17]. Notably, pleuritis was defined by the ACR criteria as the presence of a "convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion" at any time during the disease course[1]. SLEDAI-2K, also a valid measure of SLE activity, weights the severity of each manifestation and relies primarily on objective evidence of SLE activity within the preceding 10-day period[17]. Pleurisy by SLEDAI-2K is present if a subject has pleuritic chest pain with a pleural rub or effusion, or pleural thickening[17].

To address the goals of the study, the 1000 Faces database was screened for eligible patients from July 2005 to November 2007. Inclusion criteria required age ≥ 18 years and satisfaction of the revised 1997 ACR classification criteria for SLE, and completion at the first visit of an SDI and SLEDAI-2K score[1,17,20]. From a total of 1417 patients identified in this calendar period, we excluded children (n = 138), patients who did not meet ACR criteria or had missing data (n = 170), patients who had only one extractable nuclear antigen screened (n = 181), and patients missing an SDI index (n = 50) or SLEDAI-2K index (n = 2). Thus, 876 Canadian patients with lupus were studied, each of whom had at least 2 extractable nuclear antigens screened (anti-Sm, anti-Ro, anti-La, anti-RNP).

Statistical analysis. Descriptive statistics including means and standard deviations were computed. The association of demographic and clinical measures with presence (vs absence) of pleuritis was compared using the Student t test for continuous variables and chi-square test for categorical variables. Disease duration and age at diagnosis were dichotomized at the median value. Next, measures of disease activity and damage were compared between the 2 groups, including examination of modified scores for the m-ACR and m-SLEDAI-2K index. Odds ratios were calculated using logistic regression analysis to estimate the strength of association of particular demographic, clinical, and serologic features with the presence of pleuritis. Parameters initially identified as being statistically significant ($p \leq 0.05$) in the univariate analyses were entered into the multivariate regression models, to assess the independent contribution of the predictor (e.g., autoantibody) with the outcome of interest. Analyses were performed with Stata statistical software release 9 (Stata Corp., 2005, College Station, TX, USA) and Statistical Package for the Social Sciences 15 (SPSS Inc., 2006, Chicago, IL, USA).

RESULTS

Among the 876 adult patients with lupus in our study population, the mean age was 46.8 ± 13.5 years and mean disease duration 12.1 ± 9.9 years. The majority of the cohort was female (n = 795; 91%). Ethnic distribution was as follows: 569 (64.9%) were Caucasian, 103 (11.8%) Asian, 75 (8.6%) Afro-Caribbean, 50 (5.7%) Aboriginal, 42 (4.8%) were of other ethnic descent, and ethnicity was not reported in 37

(4.2%) participants. Three hundred sixty-seven patients (43%) were regular smokers.

In terms of the lupus-related profile of the study participants, the mean number of m-ACR criteria fulfilled was 5.8 ± 1.5. Further, 578 of the participants had complete SLAM-2 scores and 866 had complete SLEDAI-2K scores; the mean SLAM-2 score was 5.8 ± 4.0 and mean m-SLEDAI-2K score was 4.8 ± 4.4. Overall, about one-third of the 1000 Faces study cohort (n = 296; 34%) developed pleuritis.

In terms of autoantibody profile, 505 (58%) subjects were seropositive for anti-dsDNA antibody, 345 (39%) had anti-Ro, 250 (29%) had anti-Sm, 254 (29%) had an anti-RNP, 176 (20%) had an aPL, and 142 (16%) had anti-La antibodies.

We next focused on the predictors of pleuritis. Specifically, the association of demographic, clinical, and serologic measures with pleuritis, as well as measures of lupus disease activity and damage, was examined (Table 1). Interestingly, those with pleuritis were younger at disease presentation (mean age at SLE diagnosis 33.1 yrs vs 35.5 yrs; p = 0.009), and they experienced longer duration of disease (mean 13.6 yrs vs 11.4 yrs; p = 0.002) and greater cumulative organ system damage (mean 2.03 yrs vs 1.4 yrs; p ≤ 0.0001). Overall, the median age at SLE diagnosis was 32 years; patients with a diagnosis of SLE at ≤ 32 years of age were significantly more likely to develop pleuritis compared to those diagnosed with SLE after age 32 years (p = 0.001). The median disease duration for SLE was 10 years; patients with disease duration ≥ 10 years were significantly more likely to have pleuritis than those with a briefer disease course (p = 0.001). No significant differences by age, ethnicity, smoking status, total m-ACR, or m-SLEDAI scores were observed between SLE patients with and those without pleuritis.

The distribution of positive autoantibodies among SLE subjects with pleuritis was similar: 174/296 (59%) were seropositive for anti-dsDNA, 117/294 (40%) for anti-Ro, 105/294 (36%) anti-RNP, 104/296 (35%) anti-Sm, 55/296 (19%) aPL, and 49/294 (17%) anti-La.

In univariate analysis, seropositivity for RNP was significantly associated with pleuritis (OR 1.57, 95% CI 1.14–2.15, p = 0.005; Table 2]. Further, younger age at diagnosis of SLE, longer disease duration, and higher SDI score were also related to prevalent pleuritis. Seropositivity for

Table 1. Demographic, serologic, and disease measures according to the presence of pleuritis in the 1000 Faces of Lupus Cohort. Values are mean ± standard deviation; values rounded to nearest digit; median values were used to establish cutpoints for age at study entry, age at diagnosis, and disease duration.

Characteristics	SLE with Pleuritis, n = 296	SLE without Pleuritis, n = 580	p
Age at study entry, yrs	46.7 ± 13.9	46.9 ± 13.3	0.9
Age at SLE diagnosis, yrs	33.1 ± 12.1	35.5 ± 12.5	0.009
Disease duration, yrs	13.6 ± 10.3	11.4 ± 9.5	0.002
No. of women:men	262:34	533:47	0.1
Ethnicity*, n (%)			0.9
Caucasian	188 (33)	381 (67)	
Aboriginal	18 (36)	32 (64)	
Asian	32 (31)	71 (69)	
Afro-Caribbean	32 (43)	43 (57)	
Other or not reported	26 (33)	53 (66)	
Ever smokers**	120 (41.2)	247 (43.4)	0.6
No. of m-ACR criteria fulfilled	5.8 ± 1.8	5.7 ± 1.4	0.5
m-SLEDAI-2K score total***	5.1 ± 4.9	4.7 ± 4.1	0.3
SLAM-2 score total†	5.9 ± 4.4	5.7 ± 3.8	0.6
SDI score total	2.0 ± 2.1	1.4 ± 1.7	≤ 0.0001
Autoantibody-positive††, n (%)			
Anti-dsDNA	174 (58)	331 (57)	0.6
Anti-Sm	104 (33)	146 (26)	0.002
Anti-RNP	105 (34)	149 (27)	0.002
Anti-Sm and RNP	59 (19)	67 (12)	0.001
Anti-Ro (SSA)	117 (40)	228 (39)	0.9
Anti-La (SSB)	49 (17)	93 (16)	0.8
aPL	55 (19)	121 (21)	0.4

* May not total to 100% due to self-reported multiple ethnicities. ** ≥ 1 cigarette/day for ≥ 3 months in their lifetime (missing data from 16 subjects). *** Missing total scores from 10 subjects. † Total 578 subjects. †† Missing 2 anti-RNP, anti-Ro, and anti-La. m-ACR: modified American College of Rheumatology; m-SLEDAI-2K: modified SLE Disease Activity Index (revised); SLAM-2: SLE Activity Measure (revised); SDI: modified Systemic Lupus International Collaborating Clinics/ACR Damage Index; dsDNA: double-stranded DNA; aPL: antiphospholipid antibody or lupus inhibitor.

Table 2. Univariate and multivariate regression analyses on predictors of pleuritis in SLE.

Variable	Univariate OR (95% CI)	Multivariate 1† OR (95% CI)	Multivariate 2†† OR (95% CI)	Multivariate 3* OR (95% CI)
Age at SLE diagnosis ≤ 32 yrs vs > 32 yrs	1.58 (1.19–2.10)	1.52 (1.13–2.03)	1.52 (1.14–2.04)	1.38 (1.03–1.87)
Disease duration, ≥ 10 yrs vs < 10 yrs	1.63 (1.23–2.16)	1.33 (0.98–1.80)	1.33 (0.98–1.82)	1.39 (1.01–1.90)
SDI score	1.16 (1.08–1.25)	1.15 (1.13–2.03)	1.15 (1.07–1.24)	1.14 (1.06–1.23)
Anti-Sm antibody	1.40 (1.02–1.91)	—	0.93 (0.62–1.41)	1.29 (0.85–1.97)
Anti-RNP antibody	1.57 (1.14–2.15)	1.11 (0.74–1.65)	—	1.10 (0.72–1.70)
Concomitant RNP- and Sm-positive	1.92 (1.31–2.82)	—	—	1.98 (1.31–3.00)

† Controlling for disease duration, SDI score, age at diagnosis, and anti-RNP-only-positive (n = 874); †† controlling for disease duration, SDI score, age at diagnosis, and anti-Sm-only-positive (n = 874); * controlling for disease duration, SDI score, age at diagnosis, anti-Sm-only-positive, anti-RNP-only-positive, concomitant Sm-and RNP-positive, concomitant Sm- and RNP-negative (n = 874). SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

anti-Sm antibodies was similarly significantly related to an increase in risk of pleuritis (OR 1.40, 95% CI 1.02–1.91, p = 0.04; Table 2). Perhaps most noteworthy was that concomitant seropositivity for both RNP and Sm antibodies was identified with the greatest risk of prevalent pleuritis in these univariate analyses (OR 1.92, 95% CI 1.31–2.82, p = 0.001).

We therefore investigated in multivariate analyses which serologic profile retained a statistically significant relationship to the outcome of pleuritis. We categorized the serologic profile of the 874 patients screened for both RNP and Sm antibodies into one of 4 mutually exclusive serologic categories. Specifically, in terms of respective serologic profile, 128 (15%) patients were Sm-negative but RNP-positive; 124 (14%) were Sm-positive but RNP-negative; 126 (14%) were concomitantly Sm- and RNP-positive; and 496 (57%) patients were seronegative for both Sm and RNP antibodies (Table 3).

Most important, in these multivariate analyses, concomitant seropositivity for both RNP and Sm was related to a nearly 2-fold increase in risk of pleuritis (OR 1.98, 95% CI 1.31–3.00). In contrast, seropositivity for RNP only and for Sm only no longer retained a significant relationship with prevalent pleuritis. In addition, the other clinical and disease activity variables each remained related to prevalent pleuritis. Therefore, age at SLE diagnosis ≤ 32 years (OR 1.39, 95% CI 1.03–1.87, p = 0.03), higher SDI score (OR 1.14, 95% CI 1.06–1.23, p = 0.001), and disease duration ≥ 10 years (OR 1.38, 95% CI 1.0–1.90, p = 0.04) were each significantly associated with pleuritis (Table 2).

Table 3. Number of patients with SLE seropositive for anti-Sm and anti-RNP antibodies. The sera of 874 patient samples were screened for both RNP and Sm antibodies.

Autoantibody Status	Anti-Sm-negative	Anti-Sm-positive	Total
Anti-RNP-negative	496	124	620
Anti-RNP-positive	128	126	254
Total	624	250	874

DISCUSSION

Pleuritis has been recognized to be a prominent manifestation that contributes to substantial morbidity and heightened mortality in patients with SLE[22]. In our multiethnic Canadian study, one-third of the cohort manifested pleuritis. Further, concomitant seropositivity for both RNP and Sm autoantibodies, as well as longer disease duration, greater cumulative organ damage, and younger age at onset of SLE were each significantly associated with having pleuritis in multivariate analyses.

Previously, the frequency of SLE pleuritis across Canada was unknown. We identified prevalent pleuritis in one-third of the 1000 Faces Study, an estimate higher than that reported in Europe (16%), Spain (29%), and among symptomatic patients in China (12%)[23-25]. However, the estimated prevalence of 34% is quite similar to that reported in a pooled analysis of over 5000 SLE patients[26]. This latter study also found late-onset SLE was associated with a higher frequency of pleuritis.

Reports have previously identified that anti-RNP antibody is associated with pulmonary disease involvement, specifically pleuritis, in SLE and in other connective tissue diseases[27-30]. A report of 330 SLE patients followed in Manitoba, Canada, that overlapped in composition with some of the patients comprising our cohort, described that anti-RNP was associated with renal disease, central nervous system (CNS) involvement, and pleuritis[31].

In terms of serologic profile, anti-Sm antibodies are reported as being associated with an increase in risk of renal disease, CNS disease, and mortality in SLE[9,31,32]. In a study by Yasuma, *et al* the presence of anti-Sm antibodies was significantly associated with pulmonary fibrosis and pericardi-

tis[33]. Finally, Jurencak, *et al* showed that patients with pediatric SLE seropositive for anti-RNP, anti-Sm, anti-dsDNA, antichromatin antiribosomal P, anti-Ro, and anti-La autoantibodies are at risk for serositis[34].

In terms of potential pathophysiologic mechanisms to explain the reported serologic observations, anti-RNP antibody may play a role in the pathogenesis of tissue inflammation and injury through upregulation of inflammatory cytokine production of adhesion molecules at endothelial cells (intercellular adhesion molecule-1 and endothelial leukocyte adhesion molecule-1), via MHC class II molecule expression on endothelial cells, and by their interaction with Toll-like receptors[35]. In a mouse model of mixed connective tissue disease, immunization with U1-70 kDa RNP led to lung disease[35,36]. Finally, in the setting of mesenteric ischemic reperfusion, mice injected with anti-RNP antibodies developed pulmonary damage that occurred in a dose-dependent manner[37]. In a recent study it was suggested that dendritic cells and their subsets play a role in directing RNP autoimmunity towards pulmonary end-organ damage[38].

In addition to the reported serologic associations with RNP and Sm, we note that greater disease duration was also related to risk of pleuritis. Longer disease duration may account for the association between pleuritis and cumulative damage, inasmuch as SLE patients accrue more damage over time, including pulmonary serosal damage[5,16,39]. The lower prevalence of pleuritis reported among Chinese patients[23] compared with our study population may be explained in part by a lower mean disease duration of 7.2 years, compared to our study population mean disease duration of 12.1 years. It also seems plausible that patients with pleuritis may be more likely to receive immunosuppressive treatments, such as corticosteroids, which may lead to or be a marker for greater accrual of organ-system damage over time. We did not analyze the relationship of specific immunosuppressive medications with pleuritis in this cohort. Different genetic backgrounds and environmental exposures may explain in part the different frequencies of pleuritis found among independent cohorts.

We recognize several limitations in this study. Misclassification of pleuritis is possible. Serositis by ACR criteria includes both pericardial and pleural inflammation; thus, the prevalence of pleural inflammation may be overestimated. However, our definition of pleuritis does not differ from that of other large cohorts[16,40]. While validated indices and criteria (ACR and SLEDAI-2K) do define pleuritis in an objective manner (either by physical examination or radiographic evaluation), these definitions may still not be optimal and reliable measures of pleuritis[1,17]. The sensitivity and specificity for pleurisy defined by the ACR index are only 52% and 89%, respectively[17]. We may therefore have underestimated the amount of pleuritis in our population. Finally, medical record errors, physician or patient recall bias, and identification of more prevalent than incident cases of SLE might have had an effect on how serositis was recorded.

At the same time, the analytical approach we undertook deserves mention. We separated the cohort into 4 mutually exclusive serologic categories and were thus able to determine, in multivariate analyses, the risk of prevalent pleuritis associated with concomitant seropositivity for both RNP and Sm autoantibodies, compared to that associated with either autoantibody alone.

We found that pulmonary involvement is a common manifestation of SLE and occurred in one-third of this multiethnic Canadian cohort. Concomitant seropositivity for RNP and Sm antibodies as well as greater cumulative organ damage, longer disease duration, and younger age at onset of disease were each related to a heightened risk for prevalent lupus pleuritis. Establishing factors associated with pleuritis furnishes valuable information. We propose that seropositivity for both RNP and Sm antibodies is associated with a higher likelihood of developing pleuritis. Ultimately, we need to understand the clinical relevance of pleuritis beyond its serologic and clinical correlates and we could not do this directly in this cross-sectional study. Previous reports demonstrated a link between short-term mortality and pleuritis. Identifying SLE patients at risk for pleuritis and its consequences has been hampered in the past by a lack of predictors of pleuritis. Prospective studies are needed to determine the longterm relevance of identifying this subgroup of patients.

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