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Original Article

Clinical and Genetic Risk Factors Associated With the Presence of Lupus Nephritis

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Objective. To elucidate whether clinical features and the weighted genetic risk score (wGRS) were associated with the presence of lupus nephritis (LN). **Methods.** We retrospectively divided patients with systemic lupus erythematosus (SLE, n = 1,078) into biopsy-proven LN (n = 507) and non-LN groups (non-LN, n = 571). Baseline clinical features, serologic markers, and the wGRS were collected. The wGRS was calculated from 112 non-human leukocyte antigen (non-HLA) loci and HLA-DR β 1 amino acid haplotypes for SLE. Associations among clinical features, wGRS, and the presence of LN were identified. **Results.** In the multivariate analysis, patients with LN were younger at diagnosis (odds ratio [OR] = 0.97, $p < 0.001$), had more pleuritis (OR = 2.44, $p < 0.001$) and pericarditis (OR = 1.62, $p = 0.029$), had a higher detection rate of anti-double stranded deoxyribonucleic acid (anti-dsDNA antibodies, OR = 2.22, $p < 0.001$), anti-Smith antibodies (anti-Sm antibodies, OR = 1.70, $p = 0.002$), low level of complement (OR = 1.37, $p = 0.043$) and absence of antiphospholipid antibodies (aPL antibodies, OR = 1.60, $p = 0.002$), and had higher wGRS (OR = 1.16, $p = 0.012$). Mediation analysis suggested that anti-Sm antibodies and low complement could be mediators in the relationship between high wGRS and the presence of LN. **Conclusion.** Onset age, pleuritis, pericarditis, several serologic markers, and wGRS were associated with the presence of LN. Anti-Sm antibodies and low complement appeared to mediate the indirect relationship between wGRS and the presence of LN. **(J Rheum Dis 2021;28:150-158)**

Key Words. Systemic lupus erythematosus, Lupus nephritis, Genetic risk score, Associated factors

INTRODUCTION

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease well known for its multisystemic presentation, ranging from cutaneous manifestations to vital organ disorders [1]. Lupus nephritis (LN) is one frequent and severe organ manifestation of SLE [2] that affects 12%～69% of patients with SLE [3]. Despite current advanced treatments, LN constitutes a major cause of renal failure and is associated with reduced long-term survival [3]. Early diagnosis and treatment with immunosuppressive agents are important for improving outcomes associated with LN [4]. Thus, recognizing patients at risk for LN is advantageous for early diagnosis and prompt intervention with immunosuppressive agents, thereby reducing the mortality risk.

Previous studies have suggested that several clinical and immunologic features, such as age, sex, hypertension, malar rash, anemia, anti-double stranded deoxyribonucleic acid antibodies (anti-dsDNA antibodies), anti-Smith an-

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tibodies (anti-Sm antibodies), low complement, lupus anticoagulant [5-7], and genetic factors [8] are associated with LN. Familial and twins studies have elucidated the genetic associations of SLE [9], and large-scale meta-analyses of genome-wide association studies (GWASs) have determined a significant association between common genetic variants and disease risk for SLE [10,11]. A genetic risk score (GRS) effectively calculates the estimated effect of genetic risk on disease susceptibility, aggregating the risk loci determined in GWASs into a single measurement [12]. The weighted genetic risk score (wGRS) reflects how frequently the risk alleles were found in patients' genomes using an allelic odds ratio (OR) in a logarithmic scale [13]. A recent study demonstrated that the individual GRS for SLE can predict early disease onset and damage accrual including LN [8]. We investigated the ability of genetic risk to predict presence of LN using the wGRS calculated from the recently reported 112 non-human leukocyte antigen (non-HLA) loci and HLA-DR β 1 amino acid haplotypes [11].

Here, we investigated clinical and genetic features significantly associated with LN. Genetic risk was estimated using wGRS.

MATERIALS AND METHODS

Patients

All patients who fulfilled the American College of Rheumatology (ACR) classification criteria for SLE [14] were enrolled. All subjects provided written informed consent for inclusion in the Hanyang BAE Lupus cohort (BAE Registry of Autoimmune Diseases for Epidemiology) [15], a Korean single-center prospective observational cohort for which clinical information was updated annually from 1998～2018. This study protocol was approved by the Institutional Ethics Review Board of Hanyang University Hospital (IRB no: HYUH2001-06-001).

All patients with SLE were retrospectively classified into two groups based on renal involvement. All patients with LN were confirmed by renal biopsy before enrollment or during the follow-up period. Those who never met the ACR renal disorder criteria [14,16] before enrollment and during the follow-up period were classified as patients without LN (non-LN). Patients who met the ACR classification criteria for renal disorder but who lacked renal biopsy results were excluded from this study. A flow diagram of this study is summarized in Figure 1.

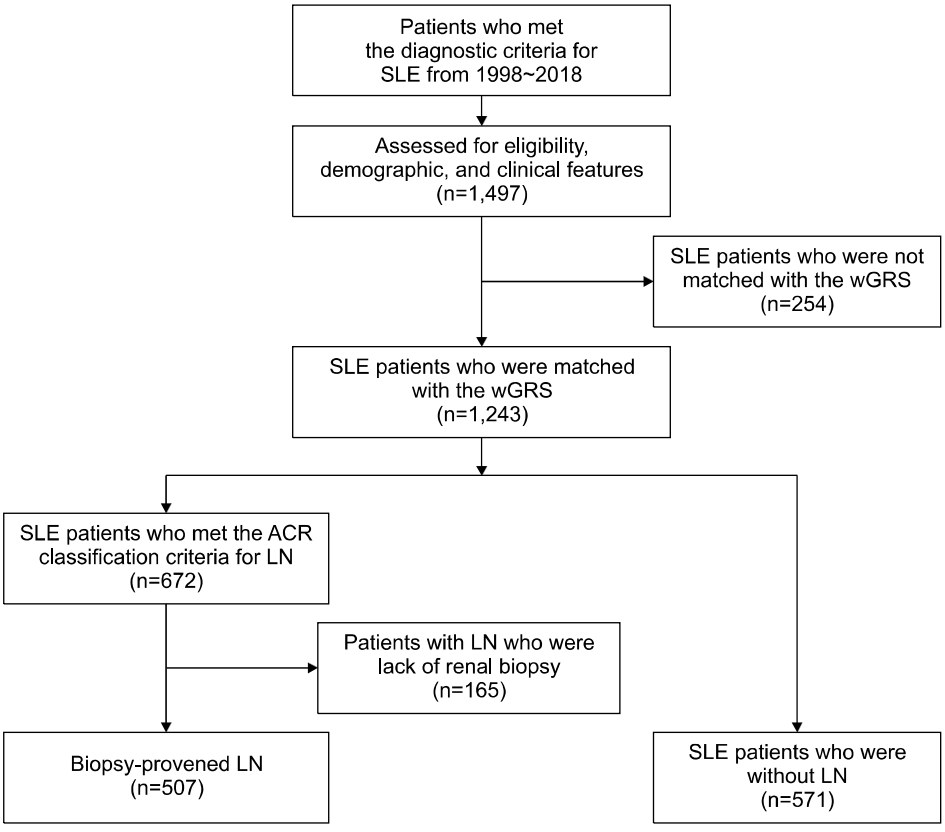

Figure 1. Flow diagram of the study design. SLE: systemic lupus erythematosus, wGRS: weighted genetic risk score, ACR: American College of Rheumatology, LN: lupus nephritis.

Clinical characteristics

Demographic and socioeconomic data were collected at enrollment. Clinical features such as the SLE Disease Activity Index-2000 [17], Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI) [18], complete blood count, chemistry, immunology, and urinalysis results were recorded and followed up at least annually.

Until 2004, histological classification of biopsy findings was based on the 1982 World Health Organization (WHO) classification for LN [19]; then, the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification was adopted [20]. Activity and chronicity indices [21,22] were also collected. If a patient with LN had undergone more than two renal biopsies, we selected the first renal biopsy result for analysis.

Calculation of the wGRS

The GRS was evaluated to elucidate its genetic effect on LN in patients with SLE. The GRS was weighted according to effect size based on the allelic odds ratio of each variant from previously reported SLE-risk loci [13], which constitute the 112 non-HLA loci of the most updated East Asian study [11] and the HLA-DR β 1 haplotypes in amino acid positions 11, 13, and 26 [23]. Finally, we used the wGRS of each patient to predict the presence of LN.

Statistical analyses

We used Student's t-test for continuous variables and the chi-square test for categorical variables of demographics, clinical characteristics, laboratory findings, and wGRS to compare the differences between the LN and non-LN groups. Logistic regression analysis was conducted to determine the associations among the demographics, clinical features, wGRS, and the presence of LN. All analyses were performed using the SAS 9.2 statistical software (SAS Institute, Cary, NC, USA). All tests were two-sided, and p-values <0.05 were considered statistically significant.

Mediation analysis has been commonly used in sociology, epidemiology [24], and clinical fields to evaluate coronary artery disease and osteoarthritis [25,26]. This method has been adopted for its ability to identify the causal relationship between an exposure and an outcome through mediators. In this study, among all of the associated clinical features of LN determined in the logistic regression analysis, we focused on serologic markers such as anti-Sm antibodies and low complement, which are objective and less affected by inter- and intrarater reliability, and assumed that they were mediators. We defined a three-step relationship among the exposure, mediators, and outcome (Figure 2). Step one was to determine the association between the wGRS and serologic markers, step two was to determine the association between the wGRS and LN, and step three was to determine the association between serologic markers and LN. If a variable was confirmed to be a mediator, all three steps should be statistically significant [27]. Furthermore, the significance of step three should be decreased with the addition of a mediator [24]. We sequentially performed logistic regression analyses on all three steps and conducted Sobel's test [27] to recertify the hypothesis. In Sobel's test statistics, absolute values over ± 1.96 were considered statistically significant.

RESULTS

Differences in demographics and clinical manifestations

A total of 1,078 patients were enrolled in this study, and all patients were of a single ethnic origin. The study population was predominantly female (n=995, 92.3%). LN was diagnosed in 507 (47.0%) patients, and 571 subjects were included in the non-LN group (53.0%) during a

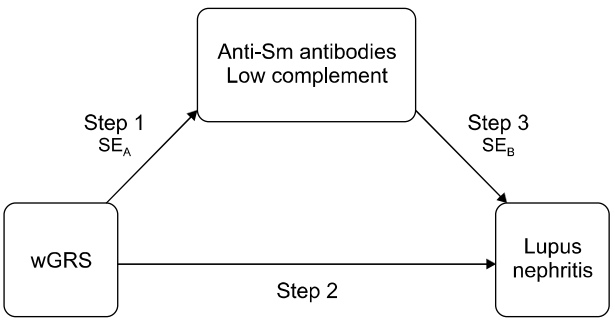

Figure 2. Conceptual model on three-step relationship between the exposure, mediator, and outcome. Step 1: association between the wGRS and serologic markers calculated by logistic regression analysis, step 2: association between the wGRS and lupus nephritis (LN) calculated by logistic regression analysis, step 3: association between serologic markers and LN calculated by logistic regression analysis, Sm: Smith, SEA: associated standard error for step 1 calculated by Sobel's test, SEB: associated SE for step 3 calculated by Sobel's test, SEA for anti-Sm antibodies: 0.066, SEA for low complement: 0.057, SEB for anti-Sm antibodies: 0.157, SEB for low complement: 0.141.

mean follow-up period of 10.4±6.1 years. Table 1 shows the clinical features based on the ACR SLE classification criteria [14] and the wGRS in the biopsy- proven LN and non-LN groups. There were fewer female patients with SLE in the LN group than in the non-LN group (n=457, 90.1% in the LN group vs. n=538, 94.2% in the non-LN group, p=0.017). Patients in the SLE group were typically diagnosed with SLE at a younger age (25.4±10.2 years vs. 29.4±11.0 years, p<0.001) and had a longer duration between SLE diagnosis and enrollment than those in the non-LN group (3.2±4.1 years vs. 2.4±3.4 years, p<0.001). Among the clinical features, the presence of a ma-

Table 1. Comparison of baseline clinical features and wGRS in patients with lupus nephritis and non-lupus nephritis

Variable	All patients (n=1,078)	LN (n=507)	Non-LN (n=571)	p-value
Sex, female	995 (92.3)	457 (90.1)	538 (94.2)	0.017
Age at diagnosis of SLE (yr)	28.0±10.8	25.4±10.2	29.4±11	<0.001*
Duration between SLE diagnosis and enrollment (yr)	2.8±3.7	3.2±4.1	2.4±3.4	<0.001*
wGRS	22.8±1.2	22.9±1.1	22.6±1.2	<0.001*
Malar rash	467 (43.4)	247 (48.7)	220 (38.6)	0.001
Discoid rash	84 (7.8)	33 (6.5)	51 (8.9)	0.172
Photosensitivity	370 (34.5)	164 (32.4)	206 (36.3)	0.288
Oral ulcer	372 (34.5)	166 (32.8)	206 (36.1)	0.196
Arthritis	698 (64.8)	324 (63.9)	374 (65.6)	0.602
Serositis	244 (22.7)	160 (31.6)	84 (14.7)	<0.001
Pleuritis	185 (17.2)	127 (25.1)	58 (10.2)	<0.001
Pericarditis	145 (13.5)	96 (19.0)	49 (9.0)	<0.001
Neurologic disorder	48 (4.5)	24 (4.7)	24 (4.2)	0.768
Immunologic disorder	934 (86.8)	466 (92.0)	468 (82.3)	<0.001
Anti-dsDNA antibodies	838 (77.8)	436 (86.0)	402 (70.6)	<0.001
Anti-Sm antibodies	207 (19.2)	124 (24.5)	83 (14.6)	<0.001
Low complement	791 (73.4)	399 (78.7)	392 (68.7)	<0.001
aPL antibodies	321 (30.0)	133 (26.2)	188 (33.0)	0.018
Hematologic disorder	885 (82.3)	428 (84.6)	457 (80.2)	0.070
Hemolytic anemia	163 (15.1)	89 (17.6)	74 (13.0)	0.045
Leukopenia	638 (59.3)	301 (59.5)	337 (59.1)	0.953
Lymphopenia	686 (63.8)	341 (67.4)	345 (60.5)	0.023
Thrombocytopenia	259 (24.0)	139 (27.4)	120 (21.0)	0.017
ANA	1,078 (100)	507 (100)	571 (100)	-
Total number of ACR criteria	5.2±1.4	5.8±1.4	4.7±1.2	<0.001*
SDI	0.3±0.7	0.4±0.9	0.3±0.6	0.001*
SDI, non-renal	0.3±0.6	0.3±0.7	0.3±0.6	0.437*
Renal biopsy classification				
II+V		2 (0.4)		
III		106 (20.9)		
III+V		68 (13.4)		
IV		226 (44.6)		
IV+V		30 (5.9)		
V		75 (14.8)		
Activity index, n=312†		7.0±4.2		
Chronicity index, n=312†		1.7±1.6		

Values are presented as mean±standard deviation, or number (%). LN: systemic lupus erythematosus patients with lupus nephritis, non-LN: systemic lupus erythematosus patients without LN, SLE: systemic lupus erythematosus, wGRS: weighted genetic risk score, dsDNA: double-stranded deoxyribonucleic acid, Sm: Smith, aPL: antiphospholipid, ANA: antinuclear antibodies, ACR: American College of Rheumatology, SDI: Systemic Lupus International Collaborating Clinics/ACR Damage Index total score at enrollment, SDI, non-renal: total score of SDI at enrollment except for the variables related to LN; such as proteinuria, pyuria, hematuria, and abnormal urinary casts. *p-values are calculated by Student's t-test and the chi-square test. p-values<0.05. †Numbers are reduced due to lack of data.

lar rash (n=247, 48.7% vs. n=220, 38.6%, p=0.001) and serositis (n=160, 31.6% vs. n=84, 14.8%, p<0.001) and immunologic abnormalities including anti-dsDNA (n=436, 86.0% vs. n=402, 70.6%, p<0.001), anti-Sm antibodies (n=124, 24.5% vs. n=83, 14.6%, p<0.001), low complement (n=399, 78.7% vs. n=392, 68.7%, p<0.001), and negative antiphospholipid antibodies (aPL antibodies, n=133, 26.2% vs. n=188, 33%, p=0.018) occurred more frequently in the LN group than in the non-LN group. In addition, with regard to hematologic disorders, hemolytic anemia (n=89, 17.6% vs. n=74, 13%, p=0.045), lymphopenia (n=341, 67.4% vs. n=345, 60.5%, p=0.023), and thrombocytopenia (n=139, 27.4% vs. n=120, 21.0%, p=0.017) were more frequently reported in the LN group than in the non-LN group. The wGRS was higher in patients in the LN group than in those in the non-LN group (22.9±1.1 vs. 22.6±1.2, p<0.001). The total number of ACR criteria and SDI score at enrollment were higher in the LN group than in the non-LN group (5.8±1.4 vs. 4.7±1.2, p<0.001 and 0.4±0.9 vs. 0.3±0.6, p=0.001). However, non-renal SDI scores were comparable between the two groups. The renal biopsy results are also summarized in Table 1. In patients with LN, the most common histologic LN classification was class IV (n=226, 44.6%), and the number of patients grew to 256 (50.5%) when classes IV and IV+V were combined. The mean activity index was 7.0±4.2 (range, 0~18) and the mean chronicity index was 1.7±1.6 (range, 0~8) in the first renal biopsy.

Factors associated with the presence of LN

Factors associated with the presence of LN are summarized in Table 2. Among the various clinical features and wGRS in the univariate analysis, younger age at diagnosis (OR=0.97, p<0.001), male sex (OR=1.78, p=0.013), longer duration between SLE diagnosis and enrollment (OR=1.06, p<0.001), presence of a malar rash (OR=1.51, p<0.001), pleuritis (OR=2.95, p<0.001), pericarditis (OR=2.49, p<0.001), hemolytic anemia (OR=1.43, p=0.037), lymphopenia (OR=1.35, p=0.020), thrombocytopenia (OR=1.42, p=0.014), anti-dsDNA antibodies (OR=2.57, p<0.001), anti-Sm antibodies (OR=1.90, p<0.001), low complement (OR=1.69, p<0.001), absence of aPL (OR=1.39, p=0.015), and higher wGRS (OR=1.24, p<0.001) were significantly associated with the presence of LN. Among aPL antibodies, negative anti-beta 2 glycoprotein I IgM antibodies (anti-β2 GPI IgM, OR=2.98, p<0.001), negative anticardiolipin antibodies (OR=1.32, p<0.001), and negative lupus anticoagulant (OR=1.61, p=0.012) test results were associated with

Table 2. Associations between clinical features and the presence of lupus nephritis

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR*	95% CI	p-value
Age at diagnosis of SLE (yr)	0.97	0.95~0.98	<0.001	0.97	0.96~0.99	<0.001
Male sex	1.78	1.12~2.82	0.013	1.51	0.91~2.50	0.112
Duration between SLE diagnosis and enrollment (yr)	1.06	1.03~1.10	<0.001	1.04	1.01~1.08	0.024
wGRS	1.24	1.12~1.38	<0.001	1.16	1.01~1.08	0.012
Malar rash	1.51	1.19~1.93	<0.001	1.08	0.81~1.43	0.581
Pleuritis	2.95	2.10~4.14	<0.001	2.44	1.65~3.60	<0.001
Pericarditis	2.49	1.72~3.60	<0.001	1.62	1.05~2.50	0.029
Hemolytic anemia	1.43	1.02~2.00	0.037	1.17	0.80~1.70	0.425
Lymphopenia	1.35	1.05~1.73	0.020	1.23	0.94~1.62	0.132
Thrombocytopenia	1.42	1.07~1.88	0.014	1.28	0.94~1.74	0.125
Anti-dsDNA antibodies	2.57	1.93~3.51	<0.001	2.22	1.59~3.10	<0.001
Anti-Sm antibodies	1.90	1.40~2.59	<0.001	1.70	1.21~2.38	0.002
Low complement	1.69	1.28~2.22	<0.001	1.37	1.01~1.86	0.043
Negative aPL antibodies	1.39	1.07~1.81	0.015	1.60	1.19~2.13	0.002
Negative anti-β2 GPI IgM antibodies	2.98	1.58~5.21	<0.001			
Negative anti-cardiolipin antibodies	1.47	1.08~2.00	0.014			
Negative lupus anticoagulant	1.61	1.11~2.34	0.012			

OR: odds ratio, OR*adjusted for age at diagnosis, sex, and the duration between SLE diagnosis and enrollment, CI: confidence interval, SLE: systemic lupus erythematosus, wGRS: weighted genetic risk score, dsDNA: double-stranded deoxyribonucleic acid, Sm: Smith, aPL: antiphospholipid. p-values and OR are calculated by logistic regression analyses. p-values<0.05.

LN. In the multivariate analysis model, younger age at SLE diagnosis (OR=0.97, p<0.001), longer duration between SLE diagnosis and enrollment (OR=1.04, p=0.024), higher wGRS (OR=1.16, p=0.012), presence of pleuritis (OR=2.44, p<0.001), pericarditis (OR=1.62, p=0.029), anti-dsDNA antibodies (OR=2.22, p<0.001), anti-Sm antibodies (OR=1.70, p=0.002), low complement (OR=1.37, p=0.043), and absence of aPL antibodies (OR=1.60, p=0.002) were statistically significant associated factors.

Relationships among the wGRS, serology, and the presence of LN

Since serologic markers, such as anti-dsDNA antibodies, anti-Sm antibodies, low complement, absence of aPL antibodies, and the wGRS were independently associated with the presence of LN and since the wGRS is an inherited trait from birth, we assumed that the wGRS could be the exposure and that serologic markers could be mediators for the presence of LN. All three of the relationships in Figure 1 were confirmed to be statistically significant (Table 3), and the statistical power of the p-values decreased when anti-Sm antibodies and low complement were added in step two (OR before adding anti-Sm antibodies in step two: 1.83, OR after adding anti-Sm antibodies in step two: 1.16, OR before adding low complement in step two: 1.60, OR after adding low complement in step two: 1.17). Through Sobel's test, we found an estimate of 2.66 for anti-Sm antibodies and an estimate of 2.17 for low complement, which were statistically significant (Figure 2, standard error $[SE]_A$ for anti-Sm antibodies: 0.066, SE_A for low complement: 0.057, SE_B for anti-Sm antibodies: 0.157, SE_B for low complement: 0.141). Based on these processes, anti-Sm antibodies and low complement appeared to have indirect effects on the relationship between the wGRS and LN.

DISCUSSION

In this study, we investigated factors associated with the presence of LN in patients with SLE. Younger age at diagnosis, longer duration between SLE diagnosis to enrollment, presence of pleuritis or pericarditis, presence or absence of certain serologic markers, and higher wGRS were independently associated with the presence of LN. In addition, anti-Sm antibodies and low complement mediated an indirect relationship between the wGRS and LN.

Several studies have reported associated clinical characteristics in patients with LN, including younger age of SLE onset [3,28], presence of a malar rash [29], hemolytic anemia [28], and thrombocytopenia [29], and increased number of fulfilled ACR criteria [29], which are in line with the findings of our study. Previous studies have also reported an association between serologic markers including anti-Sm antibodies [3,29] and anti-dsDNA antibodies [7], and the presence of LN. Our study revealed that anti-dsDNA antibodies, anti-Sm antibodies, low complement, and absent aPL antibodies were factors associated with the presence of LN after adjusting for age, sex, and duration from diagnosis of SLE to enrollment. Regarding the relationship between aPL antibodies and LN, inconsistent results have been reported [7,30-32]. One study reported that the anti-β2 GPI IgM antibodies are protective against LN [32], which is in accordance with our results. The authors postulated that a lack of data on anti-β2 GPI antibodies in past research may contribute the negative effect of aPL antibodies against LN. This inconsistent association may be due to different study designs and definitions.

The genetic components of LN have been of recent interest in the field of rheumatology [8,33,34]. Previous research using transgenic mice produced to express HLA-DR3 and develop antinuclear antibodies, an-

Table 3. Relationships among serologic markers, wGRS, and the presence of lupus nephritis

	Variables	OR	CI	p-value
Step 1	wGRS and Anti-Sm antibodies	1.27	1.11~1.46	<0.001
	wGRS and low complement	1.18	1.04~1.32	0.008
Step 2	wGRS and lupus nephritis	1.20	1.08~1.34	0.001
Step 3	Anti-Sm antibodies and lupus nephritis	1.18	1.06~1.31	0.004
	Low complement and lupus nephritis	1.19	1.06~1.32	0.002

OR: odds ratio, CI: confidence interval, wGRS: weighted genetic risk score, Sm: Smith, Step 1: association between the wGRS and serologic markers, Step 2: association between serologic markers and lupus nephritis, Step 3: association between the wGRS and lupus nephritis. p-values and OR are calculated by logistic regression analyses. p-values<0.05.

ti-dsDNA antibodies, and glomerulonephritis revealed that HLA-DR3 plays a critical role in generating an autoimmune response to anti-Sm antibodies and progressing to LN [35]. In another study, complement component 4 genes, near the major histocompatibility complex locus, reportedly generated a seven-fold variation in SLE risk [36]. Furthermore, studies have reported that anti-Sm antibodies [5] and low complement [37] are not only risk factors for LN but might also help to predict treatment response [38,39]. Based on previous research, we could reasonably assume that there is an association between serologic markers, such as anti-Sm antibodies and low complement, and LN. In this study, we revealed that anti-Sm antibodies and low complement could be mediators in the relationship between the wGRS and LN through Sobel's test. The results of our study can be explained by the assumptions of a previous study on possibility of binding of anti-Sm antibodies and complement to the kidney structure in LN [40]. It is important to determine the genetic effect of organ involvement to comprehend the pathogenesis of SLE [8]. We expect that the results of our study on the wGRS can be useful for predicting the disease course in patients with SLE in the future.

This study has some crucial limitations including insufficient data regarding the treatment regimen and treatment adherence in patients with SLE. We were unable to analyze the information on treatment because of a lack of data before enrollment and complexities of the regimen during the long follow-up period. Therefore, we focused on data that were not easily altered by treatment or disease course.

Our study also had some major strengths. First, we included a large number of patients with SLE with a relatively long follow-up period because of good patient compliance. Second, we analyzed high-validity data including clinical, serologic, histologic, and wGRS that were collected by well-trained medical staff in our center. Finally, this is the first study to determine the interactions between the wGRS and LN through the mediation of serologic markers.

As not all of the pathogenic mechanisms of LN have been elucidated, it is impossible to clearly determine the genetic background and risk factors for the presence of LN in patients with SLE. Further studies are needed to provide precision medicine for patients with LN.

CONCLUSION

Younger age at diagnosis, presence of pleuritis, pericarditis, anti-dsDNA antibodies, anti-Sm antibodies, low complement, absence of aPL antibodies, and higher wGRS were independently associated with the presence of LN in patients with SLE. Anti-Sm antibodies and low complement seemed to mediate the association between wGRS and the presence of LN.

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CONFLIC OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

J.M.S. and D.K. designed this study and drafted the manuscript. G.Y.A. assessed the clinical data and analysis. Y.C.K. and J.L. collected clinical and genetic data, and performed the statistical analysis. Y.P. advised on appropriate statistical techniques, including mediation analysis. Y.K.L., T.H.L., D.J.P., and Y.J.S. collected clinical data and interviewed patients. E.H. and K.K. analyzed the genetic data. G.Y.A., S.Y.B., C.B.C., and H.S.L. assessed the study design validity. S.C.B. designed this study and critically reviewed the manuscript.

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