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Gender differences in the clinical features and quality of life of Japanese patients with systemic lupus erythematosus: a cross-sectional study based on the LUNA registry

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Abstract

Background Gender differences in clinical manifestations and disease progression of systemic lupus erythematosus (SLE) have been well documented; however, there is a paucity of literature on the gender differences in the quality of life (QOL) of patients with SLE, especially in the context of organ-specific damage. This study aimed to explore gender differences in the clinical features and patient-reported outcomes among Japanese patients with SLE, with particular focus on the effect of joint and cardiac damage on gender-based disparities in QOL: previous studies have shown that articular and cardiac damage are associated with impaired health-related HR QOL (HRQOL).

Methods In this retrospective, cross-sectional multicenter cohort study, we used data from 1297 Japanese patients with SLE (159 males (12.3%) and 1138 females (87.7%)) enrolled in a nationwide multicenter registry (LUNA), and compared the clinical variables, organ damage scores (SLICC/ACR Damage Index [SDI]), and QOL (assessed using the LupusPRO questionnaire) between the sexes. Additionally, subgroup analyses were performed for patients with arthritis/joint damage, cardiac damage, and according to disease activity (lupus low disease activity state, LLDAS).

Results The median age of our cohort was 51 years (interquartile range, 40–63 years). Male patients had a shorter disease duration and were older at disease onset than females. The disease activity scores were slightly lower in male patients, whereas SDI was slightly higher in females. Male patients exhibited lower rates of articular/joint damage (1.26% versus 4.66%, $p=0.046$) but higher rates of cardiac damage (11.3% versus 7.15%, $p=0.015$) than females. The LupusPRO indicated higher HRQOL scores for male patients with SLE than female patients (87.4 versus 80.5, $p=0.001$); however, the difference of HRQOL became unclear between both sexes in the presence of arthritis/joint damage and cardiac damage.

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Conclusion Japanese male patients with SLE have a relatively higher HRQOL than females; however, this change became unclear in patients with SLE who had joint or cardiac damage. Further investigations are needed to clarify exact contributing factors for better HRQOL in male patients with SLE.

Keywords Gender difference, LupusPRO, Male, Quality of life, Systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by multiorgan damage resulting from complex immunological mechanisms [1]. While SLE is markedly prevalent in females (female-to-male ratio approximately 9:1), male patients often exhibit more severe clinical phenotypes, including renal, cardiovascular, and serosal involvement, as well as a greater burden of organ damage over time [2–5].

In Japan, there is a paucity of literature regarding gender-based differences in the characteristics of patients with SLE. Terao et al. [6] reported gender differences in patients with SLE using data from a nationwide registry-based financial support system (Nanbyo) provided by the Japanese Ministry of Health, Labor, and Welfare; however, the study only described SLE symptoms, making it difficult to analyze distinct clinical items, including the patient's quality of life (QOL).

Recently, Jolly et al. developed a questionnaire, LupusPRO, for evaluating the QOL of patients with SLE [7, 8]; this questionnaire system is used by specialists worldwide and can also be applied in Japan [9–11]. Because of the disease's gender prevalence, there is limited data on the QOL of male patients with SLE, with only one study by Jolly et al. using the LupusPRO questionnaire [12]. No other previous studies have described gender differences in the QOL of Japanese patients with SLE or established distinct associations between the general and/or clinical features and QOL of male versus female patients with SLE.

More importantly, it is unclear whether gender disparities in the QOL of patients with SLE exist uniformly across clinical subgroups or are influenced by specific disease manifestations. In clinical practice, organ involvement, particularly musculoskeletal and cardiovascular complications, may exert a substantial influence on QOL that exceeds the effect of demographic factors, such as sex; however, this hypothesis has not been systematically investigated.

Therefore, we investigated gender differences in the clinical features and QOL of Japanese patients with SLE using data from the Lupus Registry of Nationwide Institutions (LUNA), a multicenter registry established in Japan in 2016. Our primary objective was to determine if gender differences in QOL are fixed traits or conditionally altered by specific patterns of organ damage and disease activity.

Furthermore, the joint and cardiovascular domains were selected as focal points for analysis to examine the hypothesis that the association between gender differences and QOL is influenced by specific patterns of organ damage and disease activity. Prior studies have reported that over 90% of patients with SLE experience joint-related symptoms during the course of their illness [13]. Joint dysfunction has been consistently linked to increased pain, diminished vitality, and reduced physical functioning, all of which contribute to impaired QOL [14].

Cardiac damage, on the other hand, tends to be more prevalent among male SLE patients, with significant differences observed in our cohort. Given the substantial impact of these domains on physical QOL and long-term clinical outcomes, they were prioritized for subgroup analysis.

Additionally, because disease activity is a central therapeutic target with a well-established association with QOL, we stratified patients according to the Lupus Low Disease Activity State (LLDAS) and the Definition of Remission in SLE (DORIS) criteria, to assess whether gender-based differences in QOL persist even under controlled disease activity.

Methods

Study patients and data collection

This cross-sectional study was conducted between 2019 and 2022 using the LUNA registry, which includes data from 20 rheumatology departments of different universities and general hospitals across Japan. In the present study, we enrolled more than 1700 Japanese patients with SLE (approximately 2.5% of Japanese patients with SLE) [15, 16]. LUNA contains data from patients aged 20 years and above who were diagnosed using the revised American College of Rheumatology (ACR) criteria of 1997 for classifying SLE [17].

For the present study, we collected patient data regarding age, sex, social status (education, marriage, house income, etc.), daily habits (smoking and alcohol drinking), SLE symptoms, laboratory data, disease activity, and treatment at the time of registration. Disease activity was assessed using the Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI), whereas organ damage was assessed using the Systemic Lupus International Collaborating Clinics/ACR (SLICC/ACR) Damage Index (SDI) [18–20]. Additionally, we

investigated the QOL of patients with SLE using LupusPRO upon registration [12]. This disease-targeted tool assesses both health-related QOL (HRQOL) and non-HRQOL constructs; the HRQOL domains included data regarding lupus symptoms, cognition, lupus medications, procreation, physical health, emotional health, pain vitality, and body image, whereas the non-HRQOL domains included desires/goals, social support, coping, and satisfaction with care. The scores for LupusPRO range from 0 to 100, with higher scores indicating a better QOL [10]. In the present study, we used the Japanese version of the questionnaire [11].

Next, we collected data from SLE patients with joint damage and cardiac damage and compared their QOL measures with the respective QOL scores for male and female patients with SLE using the LupusPRO tool. Due to the limited number of patients with SDI-defined joint damage and to facilitate subgroup analysis, we combined patients with active arthritis (defined by the arthritis item in the SELENA-SLEDAI) and those with joint damage (articular/Jaccoud's arthritis defined in the SDI) into a single composite category of "arthritis/joint damage." We specifically extracted cases categorized as "articular/Jaccoud's arthritis" in the LUNA registry for this analysis; since imaging data (e.g., X-ray and MRI) were not available in the registry, joint damage was identified based on each physician's decision. Finally, cardiac damage was defined according to the SDI items and not on active disease features.

All patients participating in the LUNA registry provided written informed consent; the opt-out strategy was chosen for the individual studies. The present study was approved by the Ethics Committee of Fukushima Medical University (approval number: REC2023-050).

Statistical analysis

Continuous data were analyzed using the Mann-Whitney U test, whereas categorical data were analyzed using the Chi-squared test. All analyses were performed using Statcel4 (OMS Publishing, Saitama, Japan) or EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [21]; Statistical significance was set at $p < 0.05$.

Results

General characteristics

A total of 1776 patients were enrolled in the LUNA registry, of which 1297 patients were included in the present study (159 males (12.3%) and 1138 females (87.7%); Fig. 1). The gender-wise general characteristics of the study patients are listed in Table 1. Male patients with SLE tended to be older (48 versus 47 years, $p = 0.07$), had a shorter disease duration (8.9 years versus 11.6 years, $p < 0.001$), older age of onset (34 versus 29 years of age, $p < 0.001$), and a higher body mass index (BMI; 21.9 kg/m^2 versus 20.8 kg/m^2, $p < 0.001$) than the female patients with SLE. Moreover, male patients with SLE exhibited a significantly higher percentage of smoking and alcohol-drinking habits, and were mostly married. In contrast, complications such as Sjögren's.

syndrome and antiphospholipid syndrome were more prevalent among female patients with SLE. No statistically significant gender differences were observed in terms of household income. Likewise, there were no statistically significant differences between males and females regarding treatment therapy, considering the use of hydroxychloroquine (HCQ), prednisolone (PSL) doses,

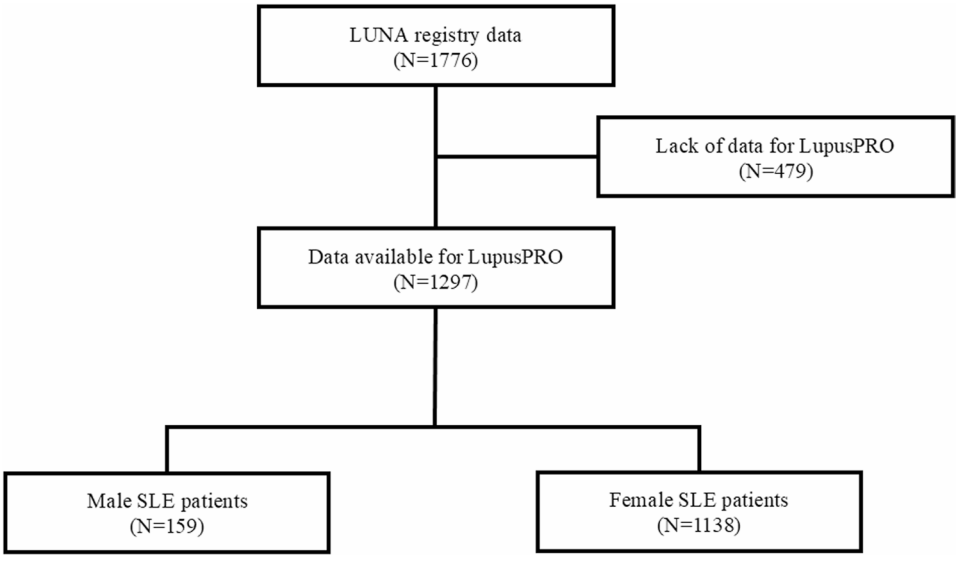

Fig. 1 Flow chart of the study

Table 1 Comparison of general characteristics and treatment between males and females in SLE patients

	Male (*N* = 159)	Female (*N* = 1138)	*p*
General characteristics			
Age, median (IQR)	48 (36.7–65.4)	47 (36.5–58.2)	0.07
Disease duration (years)	8.9 (2.76–16.5)	11.6 (4.95–20.6)	< 0.001*
Age of onset	34 (22.4–53.3)	29 (21.2–40.4)	< 0.001*
Body Mass Index	21.9 (20.3–24.4)	20.8 (19.0-23.8)	< 0.001*
LLDAS achieved	68 (42.8%)	505 (44.3%)	0.702
Sjögren's Syndrome	4 (5.2%)	152 (27.5%)	< 0.001*
Antiphospholipid syndrome	11 (14.3%)	87 (15.6%)	< 0.001*
Alcohol habit	34 (21.8%)	102 (9.2%)	< 0.001*
Smoking (current, past history)	68 (42.8%)	219 (19.2%)	< 0.001*
Marriage	57 (37.0%)	296 (27.1%)	0.011*
House income (low, below 3.0×10^6 yen/year)	55 (31.7%)	293 (30.5%)	0.766
Prednisolone dose, median (IQR)	6 (3–9)	5 (3–8)	0.200
History of mPSL pulse	64 (40.3)	432 (38.0)	0.578
Hydroxychloroquine	36 (22.6)	230 (20.2)	0.463
Immunosuppressive drugs	111 (69.8)	720 (63.2)	0.107
History of IV-CY	40 (25.2)	225 (19.8)	0.115
Mycophenolate mofetil	37 (23.3)	204 (17.9)	0.105
Mizoribine	8 (8.1)	69 (6.1)	0.618
Methotrexate	4 (2.5)	35 (3.1)	0.699
Azathioprine	12 (7.6)	90 (7.9)	0.874
Tacrolimus	59 (37.1)	204 (17.3)	0.331
Cyclosporin A	10 (6.3)	49 (4.3)	0.261
Rituximab use	1 (0.63)	11 (0.97)	0.677
Belimumab	10 (6.3)	61 (5.7)	0.77

Values are presented as medians (interquartile range: IQR) if the variables did not show a normal distribution; n (%) was used for the categorical variables

Abbreviations: *IV-CY* Intravenous cyclophosphamide pulse therapy, *LLDAS* Lupus low disease activity state

*$p < 0.05$

methylprednisolone (mPSL) pulse, and immunosuppressive agents, including cyclophosphamide.

Clinical characteristics and QOL of patients with SLE

Table 2 summarizes the data regarding laboratory results, symptoms, disease activity (SLEDAI), organ damage (including SDI), and QOL (assessed using LupusPRO) of the study patients. Male patients with SLE displayed slightly lower platelet counts and abnormal renal function than female patients. In turn, the CH50 levels were slightly decreased in the female patients, and anti-Sjögren's syndrome (SS)-A and SS-B antibody positivity was significantly lower in the male patients with SLE. Male patients had a higher frequency of International Society of Nephrology/Renal Pathology Society (ISN/RPS) Class III lupus nephritis compared with female patients (29.2% versus 19.3%, p = 0.003) [22]. However, the frequency of end-stage renal disease, proteinuria > 3.5 g/day, and reduced GFR (< 50%) was comparable between the sexes.

In terms of disease activity and symptoms, the SLEDAI scores were slightly higher in female patients than in male patients (4 versus 3, $p = 0.003$). In contrast, the frequency of common SLE symptoms was comparable between males and females, except for serositis (3.2% versus 1.1%). The assessment of organ damage accrual using SDI scores revealed that articular/Jaccoud's arthritis was more frequent in female patients with SLE (1.26% versus 4.66%, $p = 0.046$); in contrast, cardiovascular involvement was significantly more frequent in male patients with SLE (11.3% versus 2.72%, $p = 0.015$).

In terms of QOL, male patients with SLE felt good about their QOL with SLE (HRQOL: 87.4 versus 80.5, p = 0.001), and had particularly higher scores in the domains of lupus symptoms, lupus medication, procreation, pain vitality, and body image, than female patients (Fig. 2). This trend remained consistent even when the analysis was limited to patients with SLE who had a disease duration of 10 years or less. In contrast, non-HRQOL scores were similar between the two groups, with lower reporting of social support and stress coping compared with a previous report [12].

Gender differences in the QOL of patients with SLE with arthritis/joint damage and cardiac damage

In SLE, the two clinical manifestations of arthritis/joint damage or cardiac damage are known to impair daily functioning [14, 23]. We investigated gender-based differences in the QOL of patients with SLE experiencing these manifestations. Among patients with arthritis or joint damage, male patients showed higher HRQOL scores than female patients (87.2 versus 74.2), although the difference was not statistically significant (Fig. 3, Table 3). Similarly, male patients with cardiac damage tended to have higher HRQOL scores than their female counterparts (88.5 versus 80.7, p = 0.133; Table 4). In the "body image" domain, male patients scored significantly higher than females (median [interquartile range, IQR]: 100 [87.5–100] versus 75 [47.5–95], p = 0.002).

Discussion

Overall, male patients reported higher HRQOL scores compared to female patients as measured by the LupusPRO instrument. However, these differences became unclear across all clinical subgroups; the presence of joint damage or cardiac damage was associated with a tendency of higher QOL in males, but not significant between the genders. Additionally, the disease activity status, indicated by LLDAS, affected QOL in a nonlinear

Table 2 Comparison of laboratory data, activity state and quality of life (LupusRPO) in SLE patients (Male vs. Female)

	Male (*N* = 159)	**Female (*N* = 1138)**	***p***
Laboratory data			
White blood cells, median (IQR)	5900 (4350–8000)	5635 (4287–7400)	0.339
-Lymphocytes	21.3% (14.3–30.1)	19.0% (12.1–28.0)	0.026*
Hemoglobin	14.0 (12.6–15.0)	12.6 (11.4–13.5)	< 0.001*
Platelet	21.3 (17.0-25.8)	23.1 (18.4–27.8)	0.002*
Blood urea nitrogen	15.8 (13.0–20.0)	13.8 (11.0-17.4)	< 0.001*
Creatinine	0.91 (0.79–1.07)	0.67 (0.59–0.79)	< 0.001*
C3	83 (72–97)	81 (69–95)	0.399
C4	18 (13–23)	16 (11–22)	0.101
CH50	38 (27–48)	34 (16–45)	0.005*
IgG	1221 (995–1569)	1309 (1034–1615)	0.18
Anti-dsDNA ab	66 (43%)	493 (47%)	0.37
Anti-cardiolipin ab	48 (36%)	286 (31%)	0.3
Anti-SS-A ab	69 (46%)	645 (61%)	< 0.001*
Anti-SS-B ab	4 (6.3%)	102 (22%)	0.006*
Pathologic LN classification, n (%)	*N* = 65 (41.9)	*N* = 386 (35.2)	0.103
Class Ⅰ	2 (3.1)	22 (5.7)	0.64
Class Ⅱ	10 (15.4)	60 (15.6)	0.684
ClassⅢ	19 (29.2)	74 (19.3)	0.003*
ClassⅣ	16 (40.0)	135 (35.2)	0.131
Class Ⅴ	7 (10.8)	62 (16.1)	0.112
SELENA-SLEDAI			
SLEDAI scores	3 (0-5.5)	4 (2-6.75)	0.003*
NPSLE	4 (2.5)	53 (4.7)	0.214
Vasculitis	0 (0)	13 (1.1)	0.176
Myositis	0 (0)	8 (0.7)	0.289
Arthritis	20 (12.6)	187 (16.4)	0.214
Renal involvement	41 (25.8)	351 (30.8)	0.193
Skin involvement	23 (14.5)	231 (20.3)	0.08
Oral ulcer	2 (1.3)	22 (1.9)	0.554
Serositis	5 (3.2)	13 (1.1)	0.043*
Hypocomplementemia	63 (39.6)	508 (44.6)	0.233
Anti ds-DNA ab positive	45 (28.3)	329 (28.9)	0.874
Fever	5 (3.2)	24 (2.1)	0.408
Cytopenia	13 (8.2)	99 (8.7)	0.826
SDI, organ involvement (%)			
SDI scores, mean (SD)	1.47 (1.60)	1.23 (1.74)	0.011*
SDI scores, median (IQR)	1 (0–2)	1 (0–2)	0.011*
Ocular	38 (23.9)	232 (30.4)	0.307
-Cataract	32 (20.1)	209 (18.4)	0.568
Musculoskeletal	30 (18.9)	206 (18.1)	0.751
-Articular/Jaccoud's arthritis	2 (1.26)	53 (4.66)	0.046*
- Muscle atrophy or weakness	3 (1.89)	156 (13.7)	0.910
- Osteoporosis	19 (11.9)	102 (8.96)	0.225
- Avascular necrosis	15 (9.4)	84 (7.38)	0.665
- Osteomyelitis	0 (0)	1 (0.87)	0.708
Neurolopsychiatric	25 (15.7)	123 (10.8)	0.068
Renal	24 (15.1)	162 (14.2)	0.772
-GFR < 50%	21 (13.2)	143 (12.6)	0.820
-Proteinuria > 3.5 g/day	2 (1.27)	8 (0.71)	0.454
-ESRD	3 (1.89)	37 (3.25)	0.351
Pulmonary	11 (6.92)	61 (5.36)	0.422

Table 2 (continued)

	Male (*N* = 159)	Female (*N* = 1138)	*p*
Laboratory data			
Cardiovascular	18 (11.3)	70 (6.15)	0.015*
- Myocardial infarction	5 (3.14)	10 (0.87)	0.012*
- Angina	8 (5.03)	24 (2.11)	0.053
- Cardiomyopathy	2 (1.26)	9 (0.79)	0.548
- Pericarditis for more than 6 months	1 (0.63)	7 (0.62)	0.983
- Valvular disease	4 (2.51)	27 (2.37)	0.912
Peripheral vascular	9 (5.66)	60 (5.27)	0.838
Gastrointestinal	7 (4.40)	31 (2.72)	0.240
Premature gonadal failure		30 (2.64)	
Skin	13 (8.18)	88 (7.73)	0.845
Diabetes	14 (8.81)	59 (5.19)	0.064
Malignancy	3 (1.89)	45 (3.95)	0.116
LupusPRO			
LupusPRO, HRQOL	87.4 (70.9–94.8)	80.5 (65.2–90.5)	0.001*
Lupus symptoms	91.7 (66.7–100)	83.3 (66.7–100)	0.027*
Cognition	100 (68.8–100)	87.5 (62.5–100)	0.078
Lupus Medication	87.5 (50–100)	75 (50–100)	0.001*
Procreation	100 (100–100)	100 (87.5–100)	0.001*
Physical Health	100 (80–100)	95 (75–100)	0.095
Pain Vitality	85 (60–100)	80 (60–95)	0.025*
Emotional Health	75 (45.8–87.5)	72.9 (45.8–87.5)	0.198
Body Image	95 (75–100)	85 (55–100)	0.002*
LupusPRO-, non-HRQOL	48.7 (36.5–56.3)	46.9 (35.9–56.8)	0.887
Desires-Goals	81.3 (62.5–100)	81.3 (56.3–100)	0.44
Social Support	12.5 (0–50)	12.5 (0–50)	0.958
Coping	25 (4.2–50)	33 (8.3–58.3)	0.227
Satisfaction of Care	59.4 (25-87.5)	56.5 (25-81.3)	0.717

SLEDAI score was assessed upon enrollment in the LUNA registry. Values are presented as medians (interquartile range: IQR) if the variables did not show a normal distribution; n (%) was used for the categorical variables

Abbreviations: *ESRD* End-stage renal disease, *HRQOL* Health-related quality of life, *NPSLE* Neuropsychiatric systemic lupus erythematosus, *SDI* Systemic Lupus International Collaborating Clinics Damage Index, *SELENA-SLEDAI* Safety of Estrogens in Lupus Erythematosus, National Assessment-Systemic Lupus Erythematosus Disease Activity Index

*$p < 0.05$

way that varied by sex and organ involvement. These results suggest that gender differences in QOL are not fixed or inherent traits but might be influenced by organ-specific damage and disease management, emphasizing the need to consider the clinical context when interpreting patient-reported outcomes in SLE.

Gender differences in clinical features

In our cohort, male patients with SLE had an older age at the time of disease onset, a higher BMI, and a greater prevalence of smoking and alcohol consumption. Regarding organ damage accrual measured by SDI scores, cardiovascular complications were significantly more common in males, whereas articular damage, particularly Jaccoud's arthropathy, was more prevalent in females (1.26% versus 4.66%, $p = 0.046$). These patterns are generally consistent with previous reports, with several studies documenting that male patients with SLE show severe renal disease, a higher frequency of serositis, a higher positivity for anti-dsDNA antibodies, and hypocomplementemia [24, 25]. In contrast, female patients with SLE exhibit more severe skin involvement, musculoskeletal symptoms including arthritis, and oral ulcers [25]. Furthermore, male patients with SLE are more prone to increased organ damage accrual [5]. Therefore, it is important to pay attention to the patient's demographic characteristics when managing SLE, and further investigation is warranted to corroborate this.

Consistent with our findings, previous reports also demonstrated that male patients with SLE had an increased risk of cardiac events [4, 26, 27]. Mihailovic et al. [28] reported that the frequency of cardiovascular events in Swiss male patients with SLE was significantly higher than that observed in females (17% versus 4%). Notably, modifiable lifestyle factors, such as smoking and alcohol intake, as well as the frequency of use

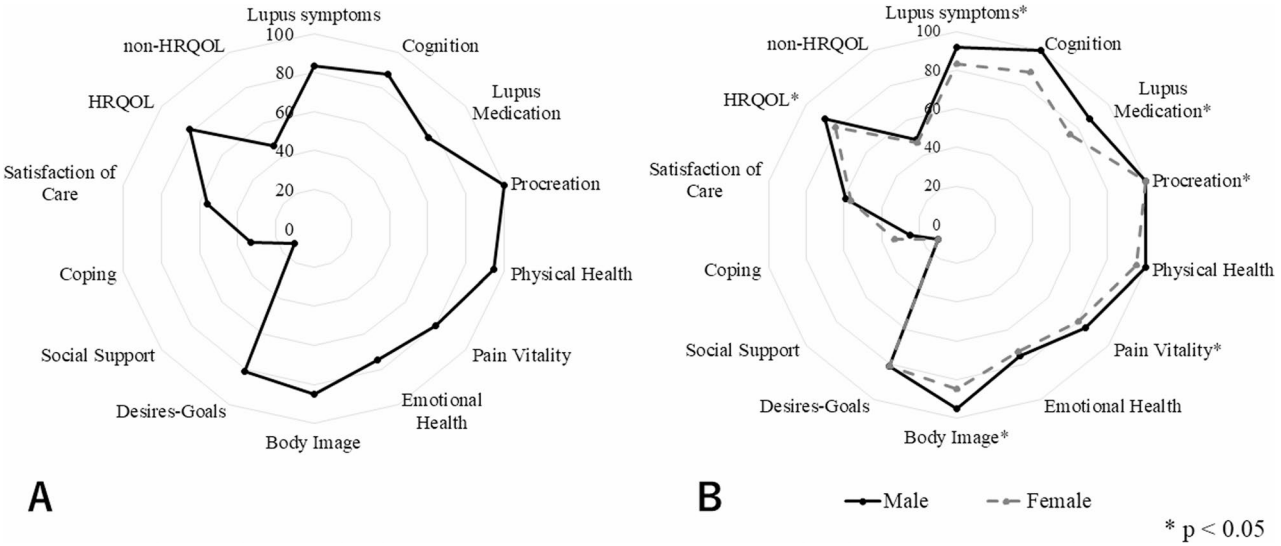

Fig. 2 Radar chart of the quality of life of patients with systemic lupus erythematosus (SLE) assessed using LupusPRO scores. **A** LupusPRO scores in all patients with SLE included in this study (n = 1297). **B** Gender differences in the quality of life of male versus female patients with SLE. Significance was set at $p < 0.05$

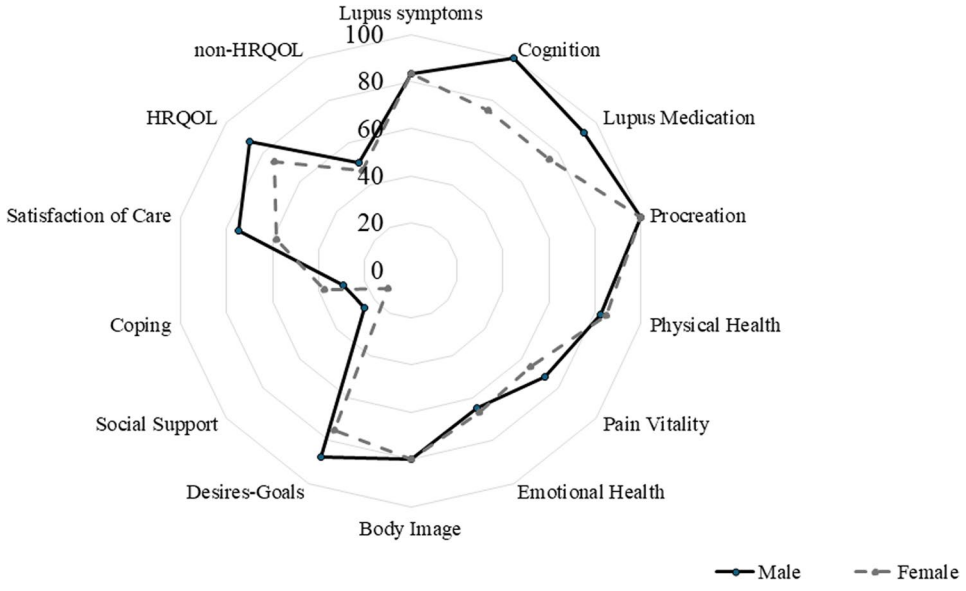

Fig. 3 Radar chart of the quality of life of patients with systemic lupus erythematosus (SLE) with arthritis/joint damage (male versus female) assessed using LupusPRO scores

of antihypertensive drugs and diabetes medications, were significantly higher in the male patients with SLE included in our study (Supplementary Table 1), suggesting an increased risk of cardiac events in males due to their lifestyle. Therefore, attention to cardiovascular events in patients with SLE is warranted not only in Western European populations but also in Japanese patients.

Regarding disease activity, female patients with SLE had higher SLEDAI scores. This is in contrast to previous reports, which have documented higher disease activity in male patients with SLE or no gender differences [4, 25]. According to a meta-analysis, the incidence of alopecia, photosensitivity, oral ulcers, and arthritis, along with lupus anticoagulant levels, was higher in female patients with SLE, whereas renal involvement, serositis/pleuritis, thrombocytopenia, and high anti-dsDNA antibody levels were more frequently seen in male patients with SLE [25]. Conversely, recent inception cohorts from China and Switzerland reported no sex-based differences in the SLEDAI scores [28, 29]. These discrepancies in results may be attributed to the following reasons. First is the difference in the population composition of the studies. In our study, at the time of registration, many outpatients

Table 3 Comparison of QOL (LupusPRO) in SLE patients with Arthritis/Joint damage (male vs. female)

LupusPRO	Arthritis/Joint damage (yes)			
	ALL (*N* = 1297)	Male (*N* = 21)	Female (*N* = 220)	*p*
Lupus symptoms	83.3 (58.3–91.7)	83.3 (50–100)	83.3 (58.3–91.7)	0.419
Cognition	75.0 (62.5–100)	100 (56.3–100)	75 (62.5–100)	0.156
Lupus Medication	75.0 (50.0-100)	93.75 (50–100)	75 (50–100)	0.088
Procreation	100 (100–100)	100 (100–100)	100 (100–100)	0.400
Physical Health	85.0 (65–100)	82.5 (65–95)	85 (66.2–100)	0.508
Pain Vitality	70 (45.0–85.0)	72.5 (37.5–88.8)	65 (45–85)	0.597
Emotional Health	66.7 (40.0-83.3)	64.6 (39.6–96.9)	66.7 (40-83.3)	0.373
Body Image	80.0 (50.0-100)	80 (60–100)	80 (45–100)	0.554
Desires-Goals	75 (50.0-93.8)	87.5 (46.9–96.9)	75 (50-93.8)	0.414
Social Support	12.5 (0–50.0)	25 (0–50)	12.5 (0–50)	0.992
Coping	33.3 (16.7–58.3)	29.1 (0-66.7)	37.5 (16.7–58.3)	0.451
Satisfaction of Care	62.5 (25.0-87.5)	75 (40.6–87.5)	58.3 (25-87.5)	0.337
HRQOL	74.4 (59.9–88.6)	87.2 (59.3–93.9)	74.2 (60-88.3)	0.160
non-HRQOL	47.7 (37.1–57.7)	50.8 (40.9–63.2)	47.1 (36.6–57.2)	0.553

Table 4 Comparison of QOL (LupusPRO) between male and female SLE patients stratified by the presence or absence of cardiac involvement

LupusPRO	Cardiac damage (yes)			
	ALL (*N* = 1297)	Male (*N* = 17)	Female (*N* = 68)	*p*
Lupus symptoms	83.3 (58.3–91.7)	83.3 (62.5–100)	75 (65.6–100)	0.810
Cognition	75.0 (62.5–100)	100 (62.5–100)	75 (59.4–100)	0.323
Lupus Medication	75.0 (50.0-100)	87.5 (43.75–100)	75 (37.5–100)	0.359
Procreation	100 (100–100)	100 (100–100)	100 (100–100)	0.078
Physical Health	85.0 (65–100)	95 (87.5–100)	90 (70–100)	0.126
Pain Vitality	70 (45.0–85.0)	80 (47.5–90)	72.5 (5.3–95)	0.956
Emotional Health	66.7 (40.0-83.3)	83.3 (47.9–91.6)	65.8 (41.3–87.5)	0.345
Body Image	80.0 (50.0-100)	100 (87.5–100)	75 (47.5–95)	0.002*
Desires-Goals	75 (50.0-93.8)	81.3 (56.3–100)	81.3 (62.5–96.8)	0.686
Social Support	12.5 (0–50.0)	0 (0-43.6)	12.5 (0-31.25)	0.791
Coping	33.3 (16.7–58.3)	25 (0-60.4)	41.7 (16.7–64.6)	0.138
Satisfaction of Care	62.5 (25.0-87.5)	88.5 (21.875–78.1)	53.1 (26.6–75)	0.834
HRQOL	74.4 (59.9–88.6)	88.5 (65.3–96.3)	80.7 (60.8–90.1)	0.133
non-HRQOL	47.7 (37.1–57.7)	44.3 (30.3–56.5)	45.6 (39.6–54.3)	0.474

Values are presented as medians (interquartile range: IQR)

Abbreviations: *HRQOL* Health-related quality of life, *LupusPRO* Lupus patient-reported outcome, *QOL* Quality of life

were included, who were mostly in the maintenance phase. Likewise, several studies enrolled patients with SLE at the time of disease onset, resulting in high disease activity [29, 30]. Second, the patients with SLE included in our study were older than those recruited in previous studies [25, 29]; the average age of our patients was in the late 40s, indicating an older population. Likewise, the average disease duration of our patients was 10 years, suggesting a long-term treatment history compared with previous studies, which may have influenced the disease activity levels [28, 29].

Impact of organ damage on QOL

A key finding of this study is that the higher HRQOL observed in male patients with SLE became unclear in patients with joint or cardiac damage. In patients with SDI-defined cardiac damage, no significant gender differences were observed in SDI domains other than "body image" (Table 4). These findings suggest that organ-specific complications might reduce the patient's overall QOL, even in male patients who otherwise tend to experience higher satisfaction.

Musculoskeletal involvement is a common manifestation of SLE, with > 90% of patients with SLE experiencing some form of joint involvement during their disease. In approximately 50% of cases, joint symptoms may present as the initial clinical manifestation of SLE [13, 31]. However, the severity and clinical presentation of joint involvement are highly heterogeneous, ranging from mild arthralgia without erosion or deformity to erosive arthritis and severe functional impairment [32]. In our cohort, the LupusPRO-based evaluation revealed that the higher HRQOL reported in male patients became unclear when the patient had musculoskeletal manifestations. The impact of musculoskeletal involvement on patient-reported outcomes in SLE has been consistently highlighted in previous studies. Shumilova and Vital [14] noted that joint pain and functional impairment were among the most prevalent contributors to decreased QOL in patients with SLE, particularly in domains such as pain, vitality, and physical functioning. Likewise, Jolly et al. [12] reported that musculoskeletal symptoms, including joint pain and stiffness, were significantly associated with lower LupusPRO scores in these domains. Another study reported that musculoskeletal damage was significantly associated with worsening of the physical

component summary (PCS) score (odds ratio, OR: 1.41; 95% confidence interval: 1.01–1.96; $p = 0.041$) [33].

In cardiac damage, recent meta-analysis noted that the strongest traditional risk factors for major adverse cardiovascular events in SLE were male gender (OR: 6.2), hyperlipidemia (OR: 3.9), familial history of cardiac disease (OR: 3.6), and hypertension (OR: 3.4) [34]. Furthermore, cardiovascular organ damage is associated with reduced HRQOL, particularly with lower scores on the physical component summary of the SF-36 [32]. Although our results did not show statistically significant differences across most LupusPRO domains in patients with SDI-defined cardiac damage, the "body image" domain score was lower in males with cardiac damage than in those without (Table 4), suggesting a possible domain-specific influence of cardiovascular damage on HRQOL. For further analysis, we investigated the possible contributing factors (distinct SDI and LupusPRO domains) which could be associated with better QOL in patients with SLE. The results were shown in Supplementary Table 2a-d. The SDI itself were associated with the higher HRQOL scores in male patients, even organ damages are present (Suppl. Table 2a). In patients with SLE having organ damage, male patients with musculoskeletal organ damage showed higher HRQOL scores than female patients. Furthermore, multivariate analysis showed that female gender is negatively associated with LupusPRO scores as well as SDI scores (Suppl. Table 2c and d). These results indicate that the gender difference can be associated with patient-reported outcome/SDI (organ damage), and higher QOL even suffered musculoskeletal damages could be associated with higher LupuPRO in male patients. However, still unmeasured factors may exist. Further investigation is needed to elucidate what distinct symptoms were clearly associated with higher QOL in male patients.

Disease activity and QOL

In our cohort, female patients exhibited a modestly higher disease activity than male patients, as reflected by the SLEDAI scores (median score: 4 versus 3, $p = 0.003$). However, this did not fully account for the observed differences in QOL, especially when stratified by the attainment of LLDAS. Even among patients who achieved LLDAS, male patients continued to report higher HRQOL scores than females in most domains (Supplementary Table 3).

The PEONY study emphasized that even lupus patients in an LLDAS state experience substantial residual disease burden, particularly in terms of pain, fatigue, and limitations in daily activities [35]. Even after achieving LLDAS, 30% of patients reported activity impairment, and 22.8% experienced reduced work productivity. These findings align with our observations and indicate that achieving LLDAS does not necessarily lead to improved HRQOL.

We also examined the impact of remission, as defined by the DORIS criteria [36]. In contrast to LLDAS, patients in DORIS remission showed no significant gender differences in HRQOL across most domains, except for "procreation." DORIS remission criteria tend to normalize HRQOL between sexes, indicating that deeper remission may be necessary to achieve equity in patient-reported outcomes (Supplementary Table 3b).

In our study, achieving LLDAS was associated with significant improvements in multiple HRQOL domains among female patients, including overall HRQOL. In contrast, male patients only showed significant improvements in the domains of pain, vitality, and emotional health, implying that the beneficial impact of LLDAS on QOL is more consistently observed in females than in males (Supplementary Table 4).

Notably, our analysis supports the notion that achieving a target low disease activity score, though important for long-term prognosis, does not necessarily guarantee improved patient-reported outcomes, particularly in the domains of physical health and vitality. This was evident as the disparity in HRQOL between the sexes persisted even among the LLDAS achievers, although attenuated by the presence of organ damage. Thus, disease activity scores and QOL measures reflect overlapping but distinct dimensions of disease burden.

Non-HRQOL issues and the sociocultural context in Japan

Beyond clinical manifestations, sociocultural factors may also contribute to the gender-related differences in QOL observed in this study. In Japan, household dynamics are affected by traditional gender roles; males are often expected to work outside the home, whereas females bear domestic responsibilities. Consequently, males spend less time on housework. The total annual working hours of males and females have decreased over time; however, in 2022, males worked an average of 404 h more per year compared with females. In families with children under 6 years of age, husbands dedicated approximately 1 h and 23 min daily to housework and childcare, whereas wives contributed 7 h and 34 min to these tasks [37]. These statistics reveal a pronounced imbalance in the household labor distribution.

In contrast to HRQOL, our study cohort recorded relatively low non-HRQOL scores compared with a previous report [12]. This situation may be specific to Japan because the conditions regarding social support, such as SLE-specific self-help resources or organizations, seem to be underdeveloped here. Inoue et al. [11] reported that only a few SLE self-help groups are functioning in Japan compared with the provision for rheumatoid arthritis patient groups. Furthermore, online

resources remain limited compared with those available for patients with rheumatoid arthritis. These findings underscore the importance of strengthening psychosocial support systems and addressing the social determinants of health, especially considering gender roles and social expectations, in the comprehensive management of SLE to ensure fairer and more personalized care for these patients.

Study limitations

First, the use of a cross-sectional study design based on an outpatient cohort in the maintenance phase of SLE may have limited the inclusion of patients with high disease activity or newly developed organ damage. Second, joint damage was defined according to the musculoskeletal domain of SDI and SLEDAI, without information on severity and imaging confirmation, such as using radiography or ultrasound. Consequently, cases of erosive or subclinical joint damage may have been underestimated and weakened the observed sex-related effects on QOL. Due to the limited number of patients with SDI-defined joint damage, particularly among males, we combined cases of active arthritis (SLEDAI) and joint damage (SDI) into a single analytic category to ensure statistical feasibility. However, the absence of detailed imaging and serological markers (such as anti-CCP antibodies and rheumatoid factor) limited the ability to distinguish between different patterns of joint pathology. Third, although subgroup analyses were conducted based on LLDAS, joint damage, and cardiac damage, multivariate adjustment for potential confounders, such as disease duration, medication use, cumulative glucocorticoid exposure, and socioeconomic status, could not be performed. Active cardiac inflammation was not systematically captured in the registry; therefore, our cardiac analyses were limited to SDI-defined cardiovascular damage. Fourth, information on occupational status, physical workload, and household responsibilities was not collected; these factors may contribute to gender differences in QOL, particularly in domains related to physical and emotional burden, social support, and coping. Fifth, we had to exclude approximately 27% of the LUNA-registered patients due to incomplete data; although this was done to ensure analytical consistency, it may have introduced selection bias. Future prospective data collection should aim to minimize missing data and assess potential bias. Finally, this study was conducted exclusively in Japanese patients using a nationwide registry. LupusPRO lacks normative data in healthy individuals; on the other hand, general population studies (EQ-5D, SF-6D) show worse pain/discomfort and anxiety/depression in women [38]. It suggests baseline sex differences may influence our results. Although this design offers a homogeneous context for analysis, it may limit the generalizability of our study findings to other ethnic or sociocultural populations. Future longitudinal analyses including multiple countries and a greater number of subjects from different ethnicities are needed to clarify the trajectory of QOL and damage accrual by gender over time.

Conclusion

In Japan, male patients with SLE tend to have a relatively higher HRQOL than females: the gender difference is associated with the QOL and might be influenced by specific organ damage or unrevealed factors: further investigation is needed to clarify the distinct association between gender differences and quality of life in Japanese patients with SLE.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13075-025-03726-1.

Supplementary Material 1.

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Authors' contributions

YS and SS designed the study, performed the analysis, and wrote the main manuscript text. YS, HE, and SS prepared the tables and figures. SS, KS, SY, HM, YF, JT, NM, TA, KN, AO, KS, YM, TS, KI, YK, RY, SO, HK, YS, MF, TK, YM, AT, YT, TO, TI, NY, and KM contributed to the revision of the manuscript. All authors have read and approved the final manuscript.

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Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to the limitations of ethical approval involving the patient data and anonymity, but may be obtained from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Fukushima Medical University School of Medicine (Approval number: General 30287). Other centers had received ethical approval from their local institutional review boards. Informed consent was obtained from all participants prior to enrollment.

Consent for publication

Consent to Publish declaration: not applicable.

Competing interests

The authors declare no competing interests.

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