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The impact of normal serum complement levels on the disease classification and clinical characteristics in systemic lupus erythematosus

Ryota Takamatsu, Yasuhiro Shimojima*, Dai Kishida, Takanori Ichikawa and Yoshiki Sekijima

Abstract

Background: Some patients have normal levels of complement during the diagnosis of systemic lupus erythematosus (SLE), although decreased serum levels of complement are a hallmark of the active phase of the disease. This study investigated the clinical characteristics, impact on the classification of SLE, and the prognosis of patients with SLE who had normal serum complement levels at initial diagnosis (N-com).

Methods: We evaluated 21 patients with N-com and 96 patients with hypocomplementemia at the initial diagnosis of SLE (H-com). The classification rates among the American College of Rheumatology (ACR) 1997, Systemic Lupus International Collaborating Clinics (SLICC) 2012, European League Against Rheumatism (EULAR)/ACR 2019 criteria, and clinical and immunological involvements were compared between SLE patients with N-com and H-com. Relapse and organ damage based on the SLICC/ACR damage index were also evaluated.

Results: The classification rates of SLE were not significantly different in the ACR, SLICC, and EULAR/ACR criteria between the N-com and H-com groups. Patients with N-com had no significant differences in the classification rates among the three criteria, whereas patients with H-com had lower classification rates in the ACR criteria than in the SLICC criteria. A lower incidence of renal manifestation, less positivity for anti-dsDNA antibody, and a higher incidence of fever were observed in patients with N-com than in those with H-com. The occurrence of relapse and organ damage was not significantly different between patients with N-com and H-com.

Conclusion: Patients with N-com were less involved in renal manifestation and anti-dsDNA antibody positivity but had a higher incidence of fever than those with H-com, while having no disadvantage in SLE classification processes. Serum complement levels at the initial diagnosis of SLE may not predict prognosis.

Keywords: Systemic lupus erythematosus, Complement, Classification criteria, Fever

Introduction

Systemic lupus erythematosus (SLE) is an inflammatory and autoimmune disorder ascribable to pleiotropic pathogenesis linked to genetic and environment factors, dysregulation in multiple factors of the immune system, hormonal imbalance, and epigenetic changes, leading to systemically visceral impairments [1, 2]. The complement system, which plays a crucial role directly in providing protection against invading pathogens and indirectly regulating innate and acquired immune responses, is also implicated in the pathogenesis of SLE [3, 4]. Moreover, the consumption of serum complement levels is typically found to be a hallmark of the active phase of SLE. In fact, the SLE Disease Activity Index (SLEDAI), which is a representative indicator of SLE disease activity, includes low serum levels of complement as a criteria [5]. Novel classification criteria, including the Systemic Lupus

*Correspondence: yshimoji@shinshu-u.ac.jp

Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan

International Collaborating Clinics (SLICC) 2012 [6] and the European League Against Rheumatism (EULAR)/the American College of Rheumatology (ACR) 2019 [7], were established based on the underlying concerns that low complement levels were excluded in the ACR 1997 criteria, even though SLE is an autoantibody and immune complex-mediated disorder [6–10]. However, some patients are found to have normal levels of complement during the diagnosis of SLE. However, it is uncertain how two novel criteria impact the classification of SLE in patients with normal serum complement levels. Serum complement levels can be affected by various physiological conditions, such as infections, traumatic damage, or immunosuppressive agents, not only in patients with autoimmune diseases but also in healthy individuals [3, 11]. Some studies have investigated the characteristics of SLE patients presenting with hypocomplementemia or the clinical differences between those with normal and low serum levels of complement [12–17]. However, those study designs broadly enrolled subjects when hypocomplementemia was observed throughout the clinical course of SLE, even after initiating treatment. Nevertheless, the clinical characteristics and prognosis of patients with normal serum complement levels at the initial diagnosis of SLE are still poorly evaluated.

This study aimed to assess the clinical characteristics, impact on the classification of SLE, and prognosis of patients presenting with normal serum levels of complement at the initial diagnosis of SLE. We compared the frequencies of fulfilling the three criteria of SLE, as well as the involved clinical and immunological items, between patients with normal and low serum levels of complement. Their prognoses, including relapse and organ damage, were also evaluated.

Materials and methods

Patients and study design

This study was retrospectively performed on patients with SLE who were diagnosed and treated between January 2010 and June 2021 in our department as a single-center study. The enrolled patients were determined when they consecutively had maintenance therapy in our department at our initiating this study. We retrospectively reviewed the clinical records of 197 patients who fulfilled the classification criteria for the initial diagnosis of SLE based on the ACR or SLICC criteria. Of these, we enrolled patients who had normal serum levels of C3, C4, and CH50 (N-com) or those who had less than normal serum levels of C3, C4, and/or CH50 (H-com). The serum levels of C3 and C4 were measured using immunonephelometry, and those of CH50 were measured using liposome immunoassay. H-com was defined as follows: C3 < 73 mg/dL, C4 < 11 mg/dL, and/or CH50 < 30 U/mL). Clinical information, including clinical and immunological items based on the SLICC criteria and their domains based on the EULAR/ACR criteria, was also extracted from the records at the initial diagnosis of SLE. Disease activity was evaluated using the SLE Disease Activity Index 2000 (SLEDAI-2K) [5]. In addition, the evaluation of relapse based on the Safety of Estrogens in Lupus Erythematosus National Assessment-SLEDAI Flare index (SFI) [18–20] and that of organ damage based on the SLICC/ACR Damage Index (SDI) [21] were also assessed during the clinical course, up to 60 months after the initial diagnosis of SLE. Organ damage was determined when the SDI score was 1 or more. Patients with insufficient clinical information for this study analyses and those with infections or malignancy at the time of SLE diagnosis were excluded from this study. Patients with H-com, in whom the targeted complement with less than the normal values at the enrollment was not measured during the observation periods, were also excluded from this study.

Statistical analyses

All data are presented as the mean ± standard deviation (SD). Two-sided p-values < 0.05 were considered statistically significant. The Mann–Whitney U test and Fisher's exact probability test were used to compare patients with N-com and H-com. The Steel Dwass test was performed for multiple comparisons among the classification criteria in patients with N-com and H-com. The Kaplan–Meier method and log-rank tests were performed as univariate analyses for relapse and organ damage between patients with N-com and H-com. Multivariable Cox regression analyses, after adjustment for an alternative potential confounder, including age, sex, SLEDAI-2K, renal disorder, or initial prednisolone (PSL) dose, were used to evaluate the associations between hypocomplementemia at the time of diagnosis and prognosis, including relapse and organ damage. Statistical analyses were performed using JMP 14.3.0 software (SAS Institute Inc., Cary, NC) and Bell Curve for Excel (SSRI, Tokyo, Japan).

Results

Classification and general activity

Of the reviewed 197 patients with SLE, 80 were excluded, because 8 had less than three types of complement for determining N-com, and 72 with H-com had insufficient clinical information. We finally included 117 patients, including 21 patients with N-com (mean age 32 years, 18 women) and 96 with H-com (mean age 37 years, 83 women) in the analyses (Fig. 1). The frequency of fulfilling the classification was not significantly different in the ACR, SLICC, and EULAR/ACR criteria, and in all the criteria together between patients with N-com and

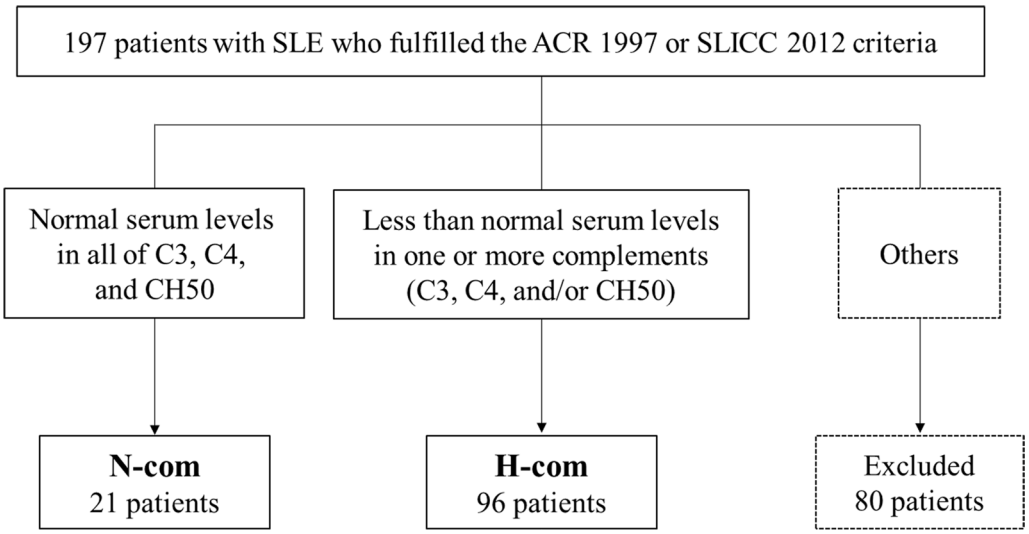

Fig. 1 Study design for enrolling patients. Of patients who fulfilled the American College of Rheumatology (ACR) 1997 or the Systemic Lupus International Collaborating Clinics (SLICC) 2012 criteria at the initial diagnosis, patients with normal serum levels of C3, C4, and CH50 (N-com) and those with lower than normal serum levels of one or more complements in C3, C4, and/or CH50 (H-com) were classified. Others: patients who were insufficient for determining N-com or H-com, those who had infection or malignancy, or those whose clinical information was insufficient for the analyses

Table 1 Classification criteria and disease activity between SLE patients with normal and low serum complement levels

	N-com (n = 21)	H-com (n = 96)	*p* value
Age, year	31.6 ± 14.1	37.2 ± 16.1	0.126
Female (%)	18 (85.7)	83 (86.5)	0.999
Fulfilled SLE classification criteria (%)			
ACR 1997	20 (95.2)	88 (91.7)	1.000
SLICC 2012	20 (95.2)	96 (100)	0.180
EULAR/ACR 2019	20 (95.2)	93 (96.9)	0.552
All three criteria	18 (85.7)	85 (88.5)	0.715
SLEDAI-2 K			
Including complement	10.8 ± 5.5	18.4 ± 8.1	< 0.001
Excluding complement		16.4 ± 8.1	0.002

SLE Systemic lupus erythematosus; *N-com* Normal serum levels of C3, C4, and CH50; *H-com* Less than normal serum levels of one or more complements in C3, C4, and/or CH50; *ACR* American College of Rheumatology; *SLICC* Systemic Lupus International Collaborating Clinics; *EULAR*, European League Against Rheumatism; *SLEDAI-2 K* SLE Disease Activity Index 2000

H-com (Table 1). In the comparisons among the three classification criteria and all of them together, patients with H-com indicated significantly higher frequency of classification in the SLICC criteria than that in the ACR or in all criteria combined ($p = 0.021$, $p = 0.004$, respectively), whereas no significant differences were observed in patients with N-com (Table 2), who had equal classification rates (95.2%) in all the three criteria (Table 1). SLEDAI-2 K was significantly lower in patients with N-com than in those with H-com, both with and without the complement item ($p < 0.001$ and $p = 0.002$, respectively).

Comparisons of clinical and immunologic items in the SLICC criteria

The mean total number of clinical and immunological items included in the SLICC criteria was significantly lower in patients with N-com than in those with H-com ($p < 0.001$), whereas that excluding the complement item was not significantly different between two groups ($p = 0.062$) (Table 3). In the clinical criteria, renal disorder was significantly less common in patients with N-com than in those with H-com ($p = 0.002$). Regarding the immunological criteria, the mean total number of immunological items was significantly lower in patients with N-com than in those with H-com ($p < 0.001$), whereas no significant difference was observed when the complement item was excluded. Positivity for anti-dsDNA antibody was significantly less observed in patients with N-com than in those with H-com ($p = 0.031$).

Comparisons of the clinical and immunologic domains in the EULAR/ACR criteria

The mean total scores of the EULAR/ACR criteria were significantly lower in patients with N-com than in those with H-com ($p < 0.001$), whereas those without the complement domain scores were not significantly different

Table 2 Statistical comparison of fulfilling SLE classification criteria in patients with normal and low serum complement levels

	In patients with N-com (n = 21)			In patients with H-com (n = 96)		
	ACR 1997	SLICC 2012	EULAR/ACR 2019	ACR 1997	SLICC 2012	EULAR/ACR 2019
ACR 1997	–	–	–	–	–	–
SLICC 2012	1.000	–	–	0.021	–	–
EULAR/ACR 2019	1.000	1.000	–	0.408	0.302	–
All three criteria	0.727	0.727	0.727	0.888	0.004	0.119

SLE Systemic lupus erythematosus; *N-com* Normal serum levels of C3, C4, and CH50; *H-com* Less than normal serum levels of one or more complements in C3, C4, and/or CH50; *ACR* American College of Rheumatology; *SLICC* Systemic Lupus International Collaborating Clinics; *EULAR* European League Against Rheumatism

between patients with N-com and H-com (Table 4). While comparing each domain, the scores of the constitutional domain (fever) were significantly higher in patients with N-com than in those with H-com ($p = 0.007$). Incidence of fever was also significantly higher in patients with N-com (n = 11 [52%]) than in those with H-com (n = 22 [23%]) ($p = 0.014$). Conversely, the renal domain scores were significantly lower in patients with N-com than in those with H-com ($p = 0.003$).

Evaluation of relapse and organ damage

Patients with N-com were administered a lower dose of corticosteroids in the initial treatment than those with H-com, although the difference was not significant (Additional file 1: Table S1). There were also no significant differences in the concomitant administration of other immunosuppressive agents between patients with N-com and H-com. The frequency of relapse-free survival was not significantly different between patients with N-com and H-com (at 5 years: 56.7 ± 13.1% vs. 61.0 ± 6.0%, $p = 0.770$) (Fig. 2a). In the analyses evaluated separately for mild/moderate flares or severe flares, no significant differences were observed between them (data not shown). The emergence of organ damage was also not significantly different between patients with N-com and H-com (at 5 years: 18.2 ± 9.7% vs. 22.5 ± 5.0%, $p = 0.741$) (Fig. 2b). No significant differences were observed in the comparisons of mean SDI during the observation periods between patients with N-com and H-com (Fig. 2c). In multivariate Cox regression analyses, after adjustment for age, sex, SLEDAI-2 K, renal disorder, or initial PSL dose, serum complement was not significantly associated with relapse or organ damage (Additional file 1: Table S2 and S3). Meanwhile, organ damage was significantly observed in patients with N-com who had hypocomplementemia during the observation periods ($p = 0.028$) despite relapse being not significantly different (Fig. 3). No significant differences in relapse and organ damage during the observation periods were not observed in patients with H-com.

Discussion

Among the ACR, SLICC, and EULAR/ACR criteria, our results showed no significant differences in their classification between SLE patients with N-com and H-com. The classification was also not significantly different among the three criteria for SLE patients with N-com. Although we employed patients classified as having SLE based on the ACR or SLICC criteria in this study, it was suggested that patients with N-com sufficiently involved clinical and immunological evidence for fulfilling the SLE classification in all three criteria. In contrast, the SLICC criteria led to a significantly higher frequency of classification than the ACR criteria in patients with H-com. Both the SLICC and EULAR/ACR criteria can strongly classify the condition by including hypocomplementemia as an alternative estimating item [6, 7], even if few essential clinical signs are insufficiently involved during an early stage of disease [22]. Given the usefulness of complement in the classification systems, our results suggest that some patients with H-com may require the inclusion of low serum complement levels as a criterion to fulfill the classification of SLE, ultimately resulting in a significantly lower classification in the ACR criteria than in the SLICC criteria.

Patients with N-com had significantly fewer inclusion items in the SLICC criteria and lower total scores in the EULAR/ACR criteria than those with H-com. These results might be associated with the significantly lower frequency of renal disorder in patients with N-com than in those with H-com. Renal disorder was found to be more intimate and crucial in SLE patients with hypocomplementemia than in those with normal complement levels [15, 23]. In addition, less positivity for anti-dsDNA antibody was also significantly demonstrated in SLE patients with N-com than in those with H-com. The SLICC classification system evaluates immunological criteria by separately adding specific autoantibodies, including anti-DNA, anti-Sm, and antiphospholipid antibodies, as pivotal biomarkers [6], effectively fulfilling the classification. Meanwhile, in the EULAR/ACR criteria, a constant score on the domain of SLE-specific

Table 3 Inclusion items in the SLICC classification criteria in patients with normal and low serum complement levels

	N-com (n = 21)	H-com (n = 96)	*p* value
Total number of items in the SLICC classification criteria, mean			
Including complement	5.3 ± 1.4	7.1 ± 1.9	< 0.001
Excluding complement		6.1 ± 1.9	0.062
Clinical items based on the SLICC classification criteria			
Total number, mean	2.9 ± 1.1	3.5 ± 1.6	0.072
Incidence in each item, n (%)			
Acute cutaneous lupus	16 (76.2)	54 (56.3)	0.139
Chronic cutaneous lupus	1 (4.8)	3 (3.1)	0.552
Oral ulcer	2 (9.5)	19 (19.8)	0.358
Nonscarring alopecia	2 (9.5)	24 (25.0)	0.155
Synovitis (2 or more joins)	15 (71.4)	51 (53.1)	0.150
Serositis	3 (14.3)	23 (24.0)	0.401
Renal disorder	1 (4.8)	39 (40.6)	0.002
Neurological disorder	0	12 (12.5)	0.121
Hemolytic anemia	2 (9.5)	16 (16.7)	0.523
Leukopenia (< 4000/mm^3)	14 (66.7)	74 (77.1)	0.402
Thrombocytopenia (< 100,000/mm^3)	4 (19.0)	25 (26.0)	0.588
Immunologic items based on the SLICC classification criteria			
Total number, mean	2.4 ± 0.7	3.6 ± 0.8	< 0.001
Number excluding complement, mean		2.6 ± 0.8	0.477
Incidence in each item, n (%)			
ANA levels			
> 80 titers	20 (95.2)	93 (96.9)	0.552
> 40 titers	21 (100)	95 (99.0)	0.999
Anti-dsDNA antibody	13 (61.9)	81 (84.4)	0.031
Anti-Sm antibody	8 (38.1)	33 (34.4)	0.803
Antiphospholipid antibody	9 (42.9)	39 (40.6)	0.999
Low complement			
Low C3	–	93 (96.9)	–
Low C4	–	83 (88.3)*	–
Low CH50	–	64 (80.0)*	–
Direct Coombs' test			
(in the absence of hemolytic anemia)	0	0*	–

N-com Normal serum levels of C3, C4, and CH50; *H-com* Less than normal serum levels of one or more complements in C3, C4, and/or CH50; *SLICC* Systemic Lupus International Collaborating Clinics; *ANA* Antinuclear antibody

*Extracted total sample numbers of C4, CH50, and direct Coombs' test because of missing values, were 94, 80, and 95, respectively

Table 4 Scores in the EULAR/ACR classification criteria between SLE patients with normal and low serum complement levels

	N-com (n = 21)	H-com (n = 96)	*p* value
Total score of the EULAR/ACR classification criteria, mean			
Including complement	19.1 ± 5.9	24.8 ± 6.9	< 0.001
Excluding complement		20.9 ± 6.9	0.266
Score of each domain in the EULAR/ACR classification criteria, mean			
Constitutional (Fever)	1.0 ± 1.0	0.46 ± 0.84	0.007
Hematologic	2.0 ± 1.8	2.5 ± 1.6	0.190
Neuropsychiatric	0	0.5 ± 1.3	0.064
Mucocutaneous	4.6 ± 2.6	3.6 ± 2.8	0.236
Serosal	0.7 ± 1.8	1.1 ± 2.1	0.423
Musculoskeletal	4.3 ± 2.8	3.3 ± 3.0	0.150
Renal	0.5 ± 2.1	3.0 ± 4.1	0.003
Antiphospholipid antibody	0.7 ± 0.9	0.8 ± 0.9	0.598
Complement	0	4.0 ± 0.2*	< 0.001
SLE specific antibodies	5.4 ± 1.8	5.7 ± 1.3	0.457

N-com Normal serum levels of C3, C4, and CH50; *H-com* Less than normal serum levels of one or more complements in C3, C4, and/or CH50; *EULAR* European League Against Rheumatism; *SLE* Systemic lupus erythematosus

*The total sample number was 95 because of missing values

antibodies can be provided when either anti-dsDNA or anti-Sm antibody positivity is observed [7]. The SLE-specific antibody scores were not significantly different between patients with N-com and H-com in the EULAR/ACR criteria because anti-Sm antibody positivity might contribute to fulfilling the domain of SLE-specific antibodies even in the absence of anti-dsDNA antibody. Nevertheless, anti-dsDNA antibody is robustly associated with the pathogenesis of lupus nephritis [24], suggesting that higher anti-dsDNA antibody positivity can be significantly associated with a higher prevalence of renal disorder in patients with H-com. SLE develops multiple manifestations depending on several pathological mechanisms, including immune complex formation and other immune processes [1]. At pathogenic sites, immune complex deposition can be mobilized from the complement in the circulating environment, especially in lupus nephritis [24–26]. Complement is activated via interaction with immune complex formation by specific antibodies, including anti-dsDNA antibody, as the critical pathogenesis of nephritis, ultimately leading to the consumption of serum levels of complement [3, 26]. Hypocomplementemia is not only a serum biomarker for estimating disease activity in patients with SLE but can also comprehensively estimate disease progression. Furthermore, increase in anti-dsDNA antibody levels, along with decrease in complement levels, can be predictively associated with deterioration in nephritis, whereas anti-dsDNA antibody can be a more sensitive biomarker than serum complement levels [23, 27]. Conversely, our results suggest that patients with N-com, in whom less anti-dsDNA antibody positive was significantly observed, may be less implicated in the development of lupus nephritis than those with H-com, resulting in a significantly lower prevalence of renal disorder.

Additionally, our result demonstrated that patients with N-com had a significantly higher incidence of fever.

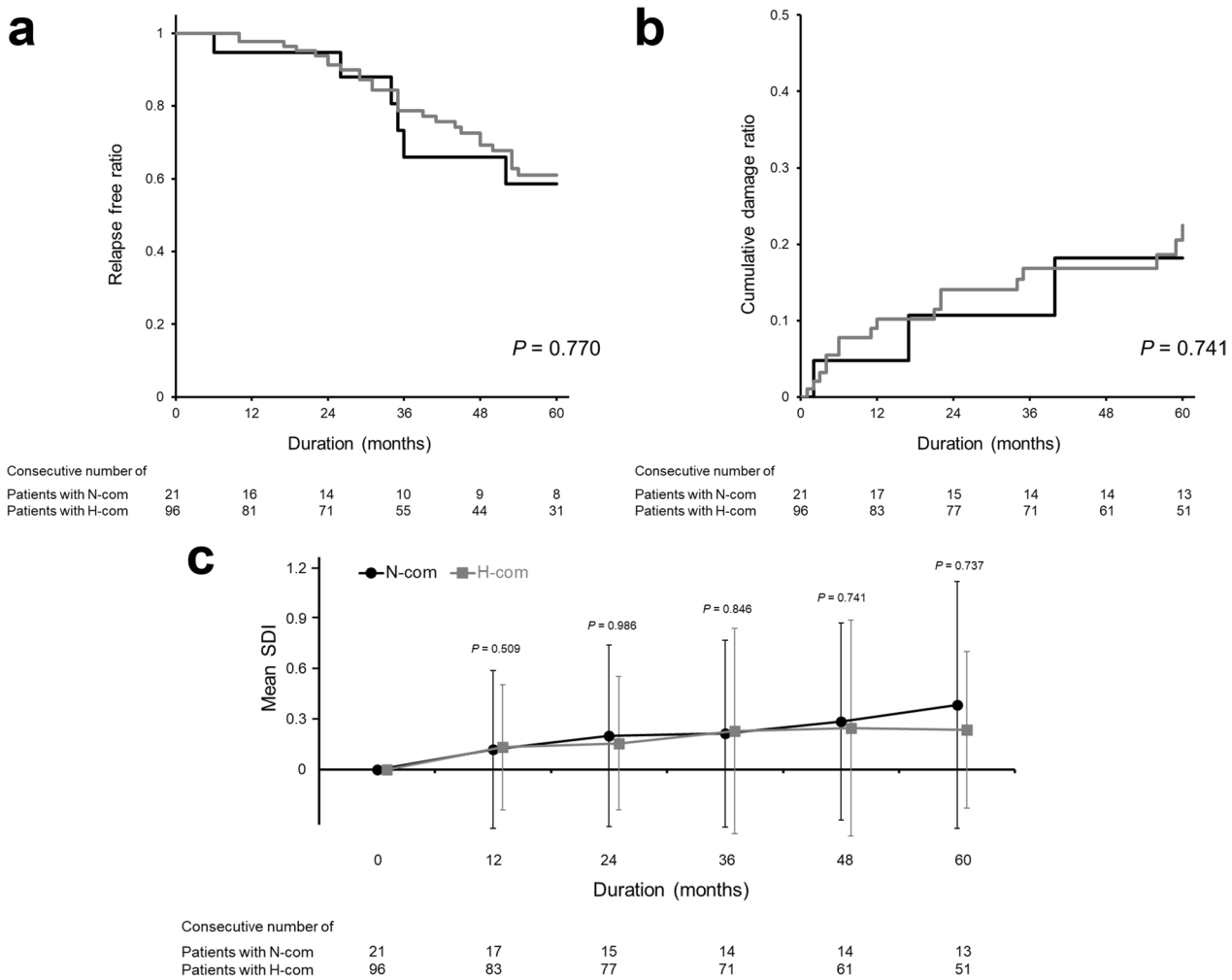

Fig. 2 Relapse and organ damage during the clinical course. Survival curves determined by the Kaplan–Meier and log-rank tests showing relapse-free ratio (**a**) and cumulative ratio of organ damage (**b**) between patients with normal serum levels of C3, C4, and CH50 (N-com, black line) and those with lower than normal serum levels of one or more complements in C3, C4, and/or CH50 (H-com, gray line). Comparisons of mean (standard deviation) the SLICC/ACR Damage Index (SDI) between patients with N-com and those with H-com during the clinical course (**c**)

The EULAR/ACR criteria have newly included fever [7] by referring a previous SLE cohort in which 53.7% of patients showed fever as an early symptom of SLE [28]. Given our results, along with the specificity of fever in SLE, patients with N-com may be in an early stage of disease, suggesting that some may develop hypocomplementemia further in their clinical course. Indeed, prevalence of hypocomplementemia has been broadly found throughout the clinical course of around 25–50% of patients with SLE [15, 29, 30]. Persistent increases in inflammatory cytokines, including interleukin (IL)-1β, IL-6, and tumor necrosis factor-α, were found to be implicated in the immune-complex formation related to the damage of target organs in SLE [24, 26], ultimately leading to hypocomplementemia. Meanwhile, these inflammatory cytokines promptly act as mediators of fever via the central nervous and endocrine systems [31, 32]. Given these pathological and physiological implications of inflammatory cytokines, it may be hypothesized that fever can be driven as the acute phase response without consumption of serum complements when inflammatory cytokines are initially produced as potential pathological mediators of SLE.

Some studies have demonstrated that persistence of low serum complement levels was associated with relapse or organ damage [12–14]. Conversely, other studies indicated that hypocomplementemia was not relevant for relapse or organ damage in the clinical course of SLE [15–17]. In our study, neither relapse nor organ damage was significantly different between

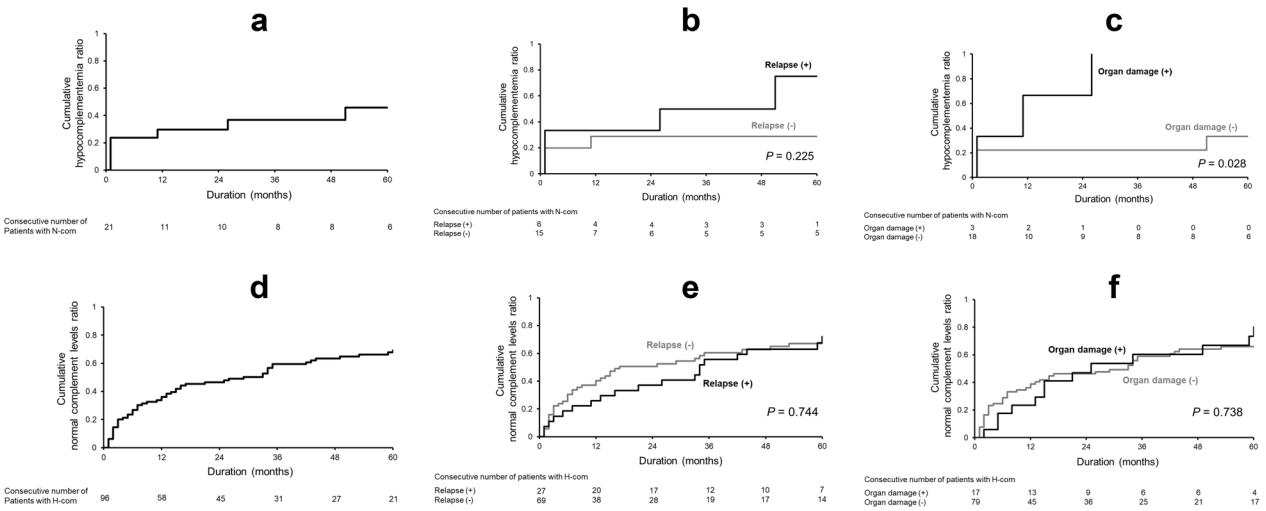

Fig. 3 Alteration of serum complement levels in the development of relapse or organ damage. Cumulative hypocomplementemia ratio in patients with normal serum levels of C3, C4, and CH50 (N-com) (**a**). Survival curves in patients with N-com determined by the Kaplan–Meier and log-rank tests showing cumulative hypocomplementemia ratio between those with relapse (black line) and those without relapse (gray line) (**b**), and between those with organ damage (black line) and those without organ damage (gray line) (**c**). Cumulative normal complement levels ratio in patients with lower than normal serum levels of one or more complements in C3, C4, and/or CH50 (H-com) (**d**). Survival curves in patients with H-com determined by the Kaplan–Meier and log-rank tests showing cumulative normal complement levels ratio between those with relapse (black line) and those without relapse (gray line) (**e**), and between those with organ damage (black line) and those without organ damage (gray line) (**f**)

patients with N-com and H-com. In addition, other factors, including initial PSL dose, renal disorder, or disease activities at the diagnosis of SLE, were not implicated in the differences in the relapse and organ damage between patients with N-com and H-com. However, organ damage was significantly observed in patients with N-com who had hypocomplementemia in their clinical course, suggesting hypocomplementemia may be implicated in developing organ damage over the clinical course. Persistent hypocomplementemia was found to be significantly related to increased incidence of renal and hematologic disorders in SLE [15]. In fact, lupus nephritis develops during the clinical course of SLE in 35–65% of patients [33, 34]. Even in hematologic disorders such as autoimmune hemolytic anemia and thrombocytopenia, recurrence can be frequently observed while maintaining immunosuppressive treatment [35, 36]. Taken together, our results suggest that normal complement levels at the initial diagnosis of SLE might not ensure a favorable prognosis. Moreover, serum complement levels at an early stage of the disease may not be a definite predictive biomarker for estimating the prognosis of SLE. Meanwhile, a decrease in serum complement levels may be implicated in the development of visceral disorders attributable to immune complex-mediated pathogenesis throughout the clinical course of SLE.

This study had some limitations. We analyzed a small number of patients from a single institution. Although we focused on serum complement levels at the initial diagnosis of SLE, these can vary with several clinical conditions throughout the clinical course. Besides, missing values of complements were observed in enrolled clinical information in this retrospective study. To better understand the relationship between serum complement levels and prognosis, it may be necessary to perform multivariable analyses with adjustment for potential confounding factors using sequential information of serum complement levels, as well as all three types of complement, in a larger number of patients with SLE. It was ultimately difficult to precisely investigate the clinical episodes appearing before diagnosing SLE in our retrospectively reviewing of the clinical records. It may be necessary to know how long the related symptoms were sustained for evaluating the implication of hypocomplementemia during the clinical stage of SLE. Hydroxychloroquine (HCQ) might be less frequently administered because of insurance coverage for that since September 2015 in Japan, although HCQ should be ideally administered as the first-line therapy [2, 37]. The evaluation of the prognosis depending on serum complement levels is also required under the standard therapeutic strategy in further study.

Conclusion

Our study suggests that patients with N-com do not have a disadvantage in the classification of SLE in the ACR, SLICC, and EULAR/ACR criteria as compared to those with H-com. Meanwhile, patients with N-com were significantly less involved in renal manifestation and anti-dsDNA antibody positivity, but had a higher incidence of fever than those with H-com. However, neither relapse nor organ damage was significantly different between patients with N-com and H-com, suggesting that serum complement levels at the initial diagnosis of SLE may not be a predictive biomarker for prognosis. Clinical information taken from a much larger sample size may be required to elucidate the usefulness of serum complement as a biomarker for the clinical course of SLE.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s42358-022-00283-y.

Additional file 1: Table S1. Initial treatment of SLE patients with normal and low serum complement levels. **Table S2.** Cox regression analysis for evaluating the implication of hypocomplementemia in relapse. **Table S3.** Cox regression analysis for evaluating the implication of hypocomplementemia in organ damage

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Author contributions
All authors made the design of this study, developed the structure and argument for this study. YS, RT, DK, TI recruited clinical data. RT and YS analyzed obtained data. YS and RT prepared the draft of this manuscript. YS contributed to revise the manuscript. All authors revised and approved of the final manuscript.

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Availability of data and materials
The data for the analyses in this study are available on reasonable request.

Declarations

Ethical approval and consent participate
This study was approved by the local ethics committee of Shinshu University (approval number: 5403).

Consent for publication
All participants provided informed consent.

Competing interests
The authors declare that they have no financial or personal competing interest.

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