Original Article

The correlation between trajectories of serum C3 variability and clinical course in Pediatric-onset systemic lupus erythematosus

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Abstract *Objective:* The aim of this study is to investigate the usefulness which 2-year trajectories of C3 variability have in predicting clinical remission and systemic corticosteroids (SCS) use in pediatric patients with systemic lupus erythematosus (pSLE).
Methods: We recruited 189 confirmed pSLE patients from the electronic database of our hospital, all had undergone SCS treatment. The follow up period was 4.17–14.83 years. We used Group-Based Trajectory modeling to divide the patients into four different trajectory groups by their initial 2-year C3 variability. We divided the patients into groups A, B or C by their clinical course and SCS use. Statistical methods included Kruskal–Wallis and Chi-square tests and logic regression test.
Results: There were 4 separate trajectories. The distribution of groups A, B and C in these 4 trajectories showed a significant difference (p = 0.005). Initial C3 and C4 levels in these 4 revealed significant differences (p $\leqq$ 0.001, p $\leqq$ 0.016). When compared to other trajectories, trajectory1 showed a higher risk for persistent SCS use (p < 0.05). The distributions of severe clinical manifestations, including proteinuria, hematuria, CNS involvement and thrombocytopenia were different in these 4 trajectories (p = 0.003). Nevertheless, none of the above manifestations contributed to the risk of persistent SCS use.
Conclusions: We have found 4 distinct C3 trajectories in pSLE patients. Distributions of clinical outcome groups were different in these 4 trajectories. Patients with trajectory1 displayed a

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higher risk for persistent SCS use, thus an earlier institution of immunosuppressant(s) and biological agents can be considered for these children.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects multiple organs.[1–4] As many as 10–20% SLE were diagnosed before the age of 18 years,[2] a condition was also known as pediatric-onset SLE (pSLE).[3] Previous studies found that pSLE patients developed more severe organ damage than adult onset patient and higher disease activity which need more intensive treatment including high dose steroid and immunosuppressive drugs.[4–7] Most of the previous studies told us that the prognosis of pSLE was poor than adult onset SLE.[5–7]

Over the years, many clinicians and researchers have attempted to determine the best treatment guidelines for patients with SLE, while even trying to predict the prognosis of patients.[1,6–8] In our previous studies, we noted that 9.1% of pediatric SLE (pSLE) patients can achieve both clinical remission and sero-reversion; and 31.3% can ever discontinue systemic corticosteroid use. However, we did not find a single predictor for the SLE children we studied.[9]

There have been many studies involving the development of group-based trajectory modeling (GBTM) in many fields. In the past decade, GBTMs have been applied in several clinical studies.[10] One article discussed applying this method in order to study the relationship between the change of fasting glucose in time and mortality in patients with diabetes mellitus.[11] Lim LSH et al. showed 5 trajectories in pSLE patients during their relatively latent clinical period by combining their SLE disease activity and prednisolone use. Their study showed the association to different damages in adulthood.[12] In this study, we attempted to establish a distinct trajectory of C3 variability in the first 2 years of pSLE patients and check the association to their future clinical outcomes and systemic corticosteroid (SCS) usage.

Patients and methods

During the period January 2006 to December 2018 we retrospectively recruited 329 patients who were diagnosed with SLE by ICD 9 = 710.0 in our hospital, a tertiary medical center in middle Taiwan. The inclusion criteria consisted of meeting the American College of Rheumatology criteria of definite SLE,[13] being followed up for more than 4 years, the intervals for available serum C3 data less than 84 days in the first 2 years after SLE diagnoses and using systemic corticosteroid (SCS) initially. We eventually recruited a total of 189 pSLE patients. This study was approved by the institutional review board of Taichung Veterans General Hospital (No. CE20204A). For the protection of privacy, the identities of the patients, physicians were scrambled in accordance with the Personal Electronic Data Protection Law.

For this study we used Group-Based Trajectory Modeling (GBTM) to classify different groups having a similar longitudinal C3 value, as well as to investigate the association between these groups and their clinical outcomes. The software used was PROC TRAJ in SAS, while Bayesian information criterion (BIC) was used to check different third-order cubic models to determine the group number. Through use of the reduced model, we then obtained the final parsimonious model to perform the analysis. The calculation to get best fit curve from C3 values in each trajectory was shown as Supplementary Material Table 1.

We then followed up each patient's clinical course and drug use until December 2020. The mean follow up period after trajectory establishment was 7.43 years (range 2.17–12.83 years). Based on the previous studies,[14,15] we divided these 189 pSLE patients into 3 groups as shown in Table 1, Group A: clinical and serology remission, involving no drugs or only hydroxychloroquine; Group B: clinical

Table 1	Definitions of outcome group A, B, C.				
	Clinical remission	Serologic remission	Steroid use	HCQ/NSAIDs use	Immuno- suppressant
Group A (number = 25) [a]Complete remission	Yes	Yes	No	Allowed	No
Group B (number = 83) Clinical/[b]laboratory remission, no steroid use	Yes	Yes/No	No	Allowed	Yes/No
Group C (number = 81)	No	No	Yes	All allowed	Yes/No

[a] Clinical remission: SLEDAI-2K = 0 under no systemic corticosteroid use.
[b] Laboratory remission: please refer to Table 2.

Table 2 Definitions of remission in laboratory data and serology.

Laboratory	
WBC (10^3/cumm)	>4000
Hgb (g/dL)	>12
Plt (/cumm)	>150000
ESR (mm/hr)	<20
CRP (mg/dL)	<0.3
C3 (mg/dL)	>87
C4 (mg/dL)	>12
GOT (U/L)	<40
GPT (U/L)	<40
Direct Coombs' test	Negative
Indirect Coombs' test	Negative
Protein/Creatinine (Urine)	<0.5
RBC(Urine) (/HPF)	0—5
WBC(Urine) (/HPF)	0—5
Protein (Urine)	Negative
Serology	
ANA	<1:160
Anti-dsDNA Ab (WHO U/ml)	<92.7
	Negative
SSA (anti-Ro)	Negative
SSB(anti-La)	Negative
Anti-Sm, RNP Ab (AU/ml)	<15
ACA IgG (GPL)	<12.5
ACA IgM (MPL)	<1.2
Lupus Anticoagulant	<20
AB2GP1 IgG (SGU)	<20
AB2GP1 IgM (SMU)	<20

remission with or without sero-reversion, involving hydroxychloroquine or NSAID or an immune-suppressant, but no SCS; and Group C: those pSLE patients who were unable to discontinue SCS even on immune-suppressants. The immune-suppressants included cyclophosphamide, azathioprine, mycophenolate mofetil, mycophenolic acid and cyclosporine. Clinical remission meant SLE disease activity index 2000 (SLEDAI-2K) = 0, or only positive anti-ds DNA antibody. Table 2 reveals our definitions of remission in both laboratory and serology data.

We performed both Kruskal—Wallis and Chi-square tests to check the distributions of groups A, B and C in the four trajectories. We used Bonferroni's adjusted *p* value to determine the statistical differences. A *p* value less than 0.05 was considered to be significant. We also analyzed the relationship of each trajectory with patient blood and serologic test values. In logistic regression for the analysis of risk factors, the variables that were statistically significant ($p < 0.05$) in the univariate model were further analyzed in the multivariable model. Odds ratios (ORs) and 95% CIs were presented. Logic regression analyses were performed with IBM SPSS Statistics Version 22 (Armonk, New York, USA).

Results

A total of 189 pSLE patients fulfilled the criteria mentioned above. The average age was 14.4 (12.1—15.9) years old. The male to female ratio was 20:169. These 189 pSLE patients were grouped as A, B and C as shown in Table 1. In Group A, (number = 25, 13.2%) patients achieved complete remission involving no drugs or only hydroxychloroquine
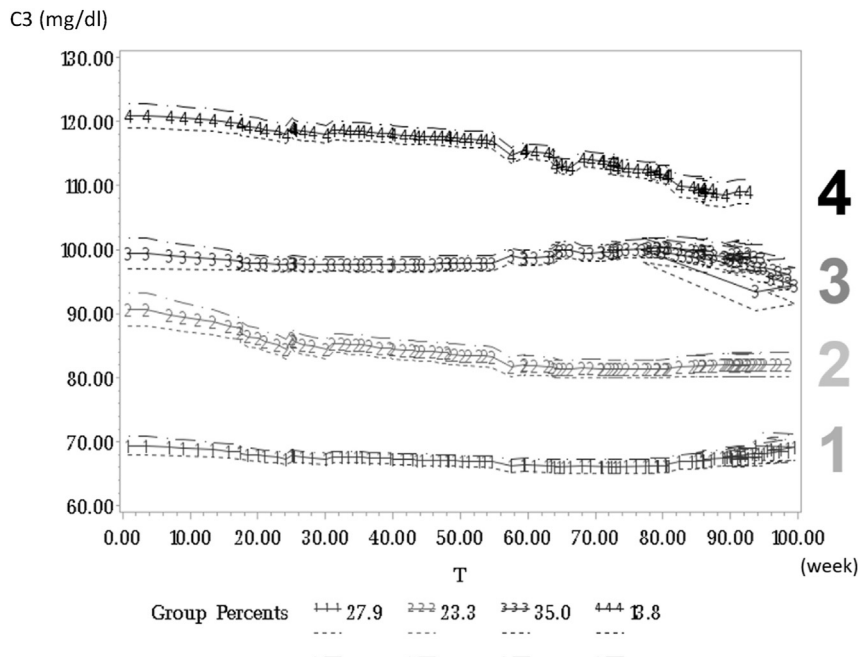

Figure 1. Four distinct C3 trajectories obtained in this study.

Table 3 Distribution of outcome groups in C3 trajectories.

Patient Group	C3 trend trajectory				p value
	1	2	3	4	
A	0 (0%)	4 (16%)	14 (56%)	7 (28%)	0.005**
B	24 (28.9%)	23 (27.7%)	26 (31.3%)	10 (12%)	**
C	29 (35.8%)	16 (19.8%)	28 (34.6%)	8 (9.9%)	**

Chi-square test, *$p < 0.05$, **$p < 0.01$.
Distribution of Group A and B in these 4 trajectories, $p = 0.002$**.
Distribution of Group A and C in these 4 trajectories, $p<0.001$**.

alone; Group B, (n = 83, 43.9%) patients experienced clinical remission involving drugs without SCS use. The remaining 81 patients (42.9%, Group C) did not achieve any level of remission and depended on long-term SCS use. The mean years (range) of the follow up periods in Group A, B, C were 8.25 (3.33—12.83), 7.12 (2.75—12.5) and 7.49 (2.17—12.17), respectively. There was no difference in follow up periods between these 3 groups.

There were 4 distinct trajectories from the longitudinal C3 values, as shown in Fig. 1. These 4 trajectories included: 1. a stable but low C3 level, 27.88%, 2. a gradual decrease in C3, 23.31%, 3. an initial elevation, then gradual decrease in C3, 35%; and 4. similar to #2, but a higher initial C3, 13.81%. These 4 trajectories could be separated individually without overlap.

In Table 3, the distribution of trajectories 1, 2, 3 and 4 in the clinical outcome groups A, B and C showed a significant difference, with $p = 0.005$. The pair comparisons shown in Table 3 revealed a significant difference between groups A and B, ($p = 0.002$), and between A and C ($p < 0.001$), but not between groups B and C ($p = 0.572$).

The 4 trajectories did show significant differences in their initial C3 levels ($p < 0.001$). In Table 4, significant differences can also be seen in the initial C4 level, the lowest C4 level ($p < 0.001$), the anti-dsDNA antibody titer ($p < 0.001$), and the lowest white blood cell counts ($p=0.001$) between these four C3 trajectories. There was a lower initial C3 level, initial C4 level, the lowest C4 level, and the lowest WBC counts in trajectory 1 than in trajectories 3 and 4 ($p < 0.05$). Trajectory 1 also had higher initial anti-dsDNA antibodies than the other 3 trajectories ($p < 0.05$). There was also a lower initial C3 level, initial C4 level and the lowest C4 level in trajectory 2 than in trajectory 4 ($p < 0.05$). However, no difference between 3 versus 4 was seen in the pair comparisons.

We also checked the clinical manifestations of high scores in SLEDAI-2K,[16] including proteinuria (PU), hematuria (HU) and CNS involvement, as well as thrombocytopenia, which requires vigorous treatment if platelet counts are <20,000/uL, though it only accounts for 1 point in SLEDAI-2K. We found that the percentage distributions of PU/HU ($p=0.001$), PU/HU + thrombocytopenia ($p = 0.026$), and the total number of patients involved in at least one of the above 4 items ($p = 0.003$) were different between these 4 TJs. In this study, we defined thrombocytopenia and CNS involvement by SLEDAI-2K; the definition of proteinuria involved protein levels ≧3+ in urinalysis and/or urine protein/creatinine levels >1.0, in addition to a daily urine protein excretion >0.5 g, which is the only definition from SLEDAI-2K. We only included those with a urine RBC >20/high power field (HPF) as hematuria, rather than an RBC >5 HPF, as defined by SLEDAI-2K.

Table 4 Age, gender, clinical manifestation and laboratory data in different C3 trajectories.

Patient group	C3 trend trajectory				p value
	1 (n = 53)	2 (n = 43)	3 (n = 68)	4 (n = 25)	
Age (years)	14.4 (12.9—15.9)	14.6 (12.1—15.6)	14.25 (11.7—15.8)	14.7 (11.4—17.0)	0.764
Gender (M:F)	8:45	2:41	10:58	0:25	
Initial C3	59.8 (39.6—73.4)	80.7 (57.8—94.2)	100 (87.9—111.6)	118 (103.5—131.0)	<0.001**
Initial C4	8.13 (4.0—11.8)	11.8 (6.9—17.5)	16.8 (11.0—23.6)	20.5 (15.9—31.0)	<0.001**
Lowest C3	38.2 (28.3—52.5)	59.6 (41.1—70.6)	81.2 (68.7—89.7)	95.3 (77.9—106.8)	<0.001**
Lowest C4	4.35 (2.5—7.1)	7.85 (3.6—11.7)	13.45 (7.0—17.2)	17.5 (12.5—20.9)	<0.001**
Initial Anti-dsDNA Ab	65.9 (33.3—200.6)	28 (12.0—86.3)	16.2 (8.5—33.6)	15.5 (9.7—30.3)	<0.001**
Lowest WBC	3000 (2305—3900)	3400 (2700—4500)	4060 (3000—4982.5)	3800 (3200—4800)	0.001
PU[a]/HU[b]	31 (58.5%)	22 (51.2%)	19 (27.9%)	6 (24.0%)	0.001**
Low platelet[c](Lp)	19 (35.8%)	11 (25.6%)	11 (16.2%)	7 (28.0%)	0.102
PU/HU + Lp	12 (22.6%)	9 (20.9%)	4 (5.9%)	2 (8.0%)	0.026*
CNS[d]	4 (7.5%)	2 (4.7%)	6 (8.8%)	1 (4.0%)	0.778
PU/HU + Lp + CNS	42 (79.2%)	26 (60.5%)	32 (47.1%)	12 (48.0%)	0.003**

[a] PU: proteinuria (protein≧3+ in urinalysis and/or urine protein/creatinine >1.0).
[b] HU: hematuria, RBC≧20/high power field in urinalysis, exclude the menstruation condition.
[c] Low platelet: platelet count <100,000/mm³. PU/HU+Lp: patients had both proteinuria/ hematuria and low platelet count.
[d] CNS: central nervous system involvement, including seizure, psychosis, headache, vasculitis, cerebrovascular accident and organic brain syndrome.
Kruskal—Wallis test. Medain (IQR).
*$p < 0.05$, **$p < 0.01$.

Table 5 Odds ratio of outcome group C in the four trajectories.

	Univariate			Multivariable		
	OR	95% CI	P value	OR	95% CI	P value
Age	0.9628	0.8773 1.0567	0.4244			
Initial C3	0.9940	0.9849 1.0032	0.2028			
Initial C4	0.9941	0.9630 1.0261	0.7127			
Lowest C3	0.9931	0.9819 1.0044	0.2335			
Lowest C4	0.9915	0.9500 1.0347	0.6937			
Lowest ANA	1.0003	0.9999 1.0007	0.1669			
Anti-ds DNA	1.0001	0.9975 1.0027	0.9472			
WBC lowest	1.0002	1.0000 1.0004	0.0271*	1.0003	1.0001 1.0005	0.0067*
Initial-Lowest C4	0.9940	0.9348 1.0569	0.8465			
Initial C4/C3	5.8681	0.1094,314.6619	0.3838			
[a]PU	1.1498	0.6235 2.1205	0.6548			
[b]HU	0.8782	0.4704 1.6396	0.6835			
[c]Low plt	0.8348	0.4284 1.6270	0.5959			
PUHU + low plt	0.9036	0.3947 2.0685	0.8104			
[d]CNS	0.3392	0.0914 1.2582	0.1060			
Any	0.9163	0.5133 1.6357	0.7674			
Trajectory group						
1	Reference			Reference		
2	0.4904	0.2157 1.1152	0.0892	0.4190	0.1791 0.9807	0.0450*
3	0.5793	0.2805 1.1962	0.1400	0.4267	0.1952 0.9328	0.0328*
4	0.3895	0.1434 1.0579	0.0644	0.2922	0.1034 0.8260	0.0203*

[a] PU: proteinuria (protein≧3+ in urinalysis and/or urine protein/creatinine >1.0).
[b] HU: hematuria, RBC≧20/high power field in urinalysis, exclude the menstruation condition.
[c] Low platelet: platelet count $<100,000/mm^3$. PU/HU+Lp: patients had both proteinuria/ hematuria and low platelet count.
[d] CNS: central nervous system involvement, including seizure, psychosis, headache, vasculitis, cerebrovascular accident and organic brain syndrome.
*$p<0.05$, **$p<0.01$.

Multi-variable analysis shown in Table 5 reveals a significantly lower risk of persistent SCS use (Group C) in trajectory 2 (OR = 0.42, 95%CI = 0.18−0.98, p = 0.045), trajectory 3 (OR = 0.43, 95%CI = 0.20−0.93, p = 0.033), and trajectory 4 (OR = 0.29, 95%CI = 0.18−0.83, p = 0.020), when compared to trajectory 1. As shown in regression analyses, neither PU, HU, thrombocytopenia nor CNS involvement contributed to the risk of persistent SCS use.

Discussion

From our study, through using initial 2-year C3 follow up data, we have established 4 distinct C3 trajectories in pSLE. These 4 trajectories showed different distributions in the clinical courses grouped as A, B and C during the subsequent 7.43 years, with trajectory 1 showing a higher risk for persistent SCS use. Nevertheless, those significant pSLE clinical manifestations, which included PU, HU, CNS involvement and thrombocytopenia cannot predict the persistent SCS use, although the percentage distributions of PU/HU with or without thrombocytopenia did show a difference in these 4 trajectories.

In other studies, single or multiple variants with anti-dsDNA, ANA, C3, C4, proteinuria, or SLEDAI had been used to predict outcomes of pSLE patients.[5,7,8,16,17] However, ours is the first study using GBTM of longitudinal C3 varieties in the initial 2 years as trajectories to predict disease remission and persistent SCS use in pSLE.

Most of the previous studies have determined that the prognosis of pSLE was worse than that of adult onset SLE.[18−20] In spite of all the advancements in medical science, long-term remission in SLE patients remains rare,[19−21] as remitted patients usually experience a relapse after variable periods of remission. Hermine I. et al. found that pSLE patients developed more severe organ damage than adult-onset patients, and also experienced higher disease activity which required more intensive treatment involving high doses of steroids and immunosuppressive drugs.[3] With the advent of immunosuppressant and biological agents,[22,23] finding those high risk pSLE patients and providing for them an earlier institution of these non-SCS agents becomes an important task for pediatric rheumatologists.

There has been only one trajectory study involving pSLE, and it involved the use of longitudinal SLE disease activity (SLEDAI-2K) and daily prednisolone dosages to establish 5 trajectories to predict outcomes during adulthood.[12] In that study 45.5% of patients revealed a chronically low disease activity (TJ class 5), which was higher than other courses, and included late relapse (TJ class 4, 19.5%), moderate initial activity with long-term low activity (TJ class 3, 16.7%), high initial activity with long-term low activity (TJ class 2, 12.1%) and relapsing/transforming (TJ class 1, 6.3%). After several overlaps in terms of SLEDAI-2K were

noted over the course of 5 years, and prednisolone dosage for a period of 7.5 years was noted, the 5 trajectories showed different trends in damage occurrence. Our study focused on C3 trends during the first two years. In contrast to the overlaps of trajectories from SLE activity and daily SCS use in the previous study, the 4 trajectories from our C3 variability showed a distinct trend. These 4 trajectories showed differences in terms of the rate of PU, HU and persistent SCS use. CNS involvement contributed a high weight in SLEDAI- 2K, however these 4 trajectories showed a similar distribution of CNS involvement. Thrombocytopenia often requires high dose SCS, and even pulse therapy for those patients with platelet counts less than 20,000/uL. After analysis of the results taken from our data, thrombocytopenia was neither associated with different C3 trajectories nor persistent SCS use. In the 5-trajectory study, patients of different ethnicities were involved, included 181 Asians. The pSLE patients of Asian descent showed a higher probability of having TJ classes 2 and 3 than TJ class 5, when compared to Caucasians and other minorities. In our study all pSLE patients were Asian, and the patient number (189) was comparable to previous pSLE trajectory study (n = 181). From the above information, our C3 trajectory is able to identify those SCS dependent pSLE patients earlier, no matter the presence of PU, HU, CNS involvement or thrombocytopenia, at least in an Asian population.

We thoroughly checked the four manifestations, PU, HU, CNS involvement and thrombocytopenia in each C3 trajectory. However, we were unable to find different distributions in the A, B and C groups within all C3 trajectories (Table 1, Supplementary data). From Table 2 under Supplementary data, the percentage of patients having at least one of the four manifestations mentioned above was different in groups A, B and C ($p = 0.007$). Being different from our expectations regarding this aspect, group B had 69.9% of patients, higher than both groups C (55.6%) and A (36%).

Complement system has been shown to accelerate several steps in SLE pathogenic pathways, including enhance the autoantigen formation after cell apoptosis, loss of tolerance and release of cytokines, especially interferon-α.[24] While complement activation is a hallmark of SLE pathogenesis and decreased C3 is associated with renal and hematological diseases, decreased complement levels are not consistently associated with disease flare up.[25] There are several factors influencing the serum complement levels, including the individual genetic polymorphisms, individual variability in breakdown/production of complement proteins, and various tissue deposition amount of complement, for example, glomerular membrane.[24] The individual variations above can be better fitted by a trend timeline, i.e., trajectory analysis.[26]

The limitation of this study is lower percent (51.2%) of pSLE patients with initial low C3 levels. In a French multi-center study for pSLE, there were 78% patients with initial lower C3 levels.[27] The major reason can be the bias from recruiting patients followed up at least for 4 years in this study. As mentioned in "patients and methods", there were 329 pSLE patients and 75% of these patients had initial lower C3 levels, the rate was higher than the study group ($p < 0.00001$). Excluding those followed up less than 2 years, there were 253 pSLE patients, and 63% had initial lower C3 levels, the rate was still higher than the study group ($p = 0.008$).

In conclusion, GBMT can provide clinicians and researchers with a new method for assessing disease progression by timing of a single variable or multiple variables. It can assist clinicians in adopting different treatment strategies for different patients with pSLE. Additionally, C3 trajectory may assist in patient inclusion during any future clinical trials.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2023.07.007.