Clinical spectrum and prognosis of SLE-associated severe thrombopenia: A single-center review of 162 treatment-naïve patients

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Research Article

Abstract

Background

Severe thrombocytopenia (TP) is a common manifestation of systemic lupus erythematosus (SLE) that increases the risk of accruing damage and mortality. This study aimed to describe the demographic features, clinical characteristics, laboratory findings and outcomes of a large series of treatment-naïve SLE patients with severe TP and explore the factors influencing prognosis in patients with SLE-associated TP.

Methods

The study enrolled treatment-naïve SLE patients complicated with severe TP who were older than 14 years old and admitted to our hospital between November 2010 and November 2018. Demographic, clinical and laboratory data were collected retrospectively between October 2019 and February 2020.

Results

TP occurred in 31.83% of SLE patients, of whom 37.80% had severe TP. 162 treatment-naïve SLE patients complicated with severe TP were included in the analysis, including 17 males. The clinical and laboratory features are shown in Table 1–2. The treatment responses are displayed in Table 3–4, and the parallel program model is shown in Fig. 1. Multivariate analysis of the risk factors is shown in Table 5.

Conclusions

In patients with SLE-associated TP, male and older age predicted the lack of a response, serositis predicted the lack of a complete response, and anti-Sm antibodies predicted a response in week 1. Advanced age predicted the lack of a complete response at week 4, and anti-nRNP antibodies and anti-SSB antibodies predicted a complete response. Advanced age, myositis and anti-Ro antibodies predicted the lack of a response at week 24, and leukocytopenia predicted the lack of a complete response. Pulmonary arterial hypertension was predictive of serious infections. Myositis and leukopenia were predictive of mortality. Advanced age and mucocutaneous hemorrhage predicted the lack of a low-dose glucocorticoid complete response (LDG-CR), while anti-nRNP antibodies were predictive of LDG-CR.

Background

SLE is a prototypic autoimmune disease that can affect any organ or tissue. When the circulatory system is involved, it can cause leukopenia, anemia, and thrombocytopenia (TP)(1). TP is a common manifestation of SLE that increases the risk of accruing damage and mortality(2, 3). When patients'

platelet (PLT) counts are below $30*10^9$/L, their risk of visceral bleeding is elevated, and they are more likely to complain of fatigue and obviously impaired quality of life.

The pathophysiology of SLE-associated TP remains incompletely understood. There are three potential mechanisms: a reduced production of PLTs in the bone marrow, the sequestration of PLTs in the spleen or the premature destruction of PLTs in the spleen, liver and peripheral circulation. The traditional understanding is that PLTs are prematurely destroyed in the spleen and liver after being coated with autoantibodies (4). Autoantibodies can also induce megakaryocyte dysfunction(5). In recent years, other hypotheses have been proposed, which mainly involve T cells(6–8). Scofield et al. found that TP was associated with antiphospholipid antibodies (aPL), antiribonucleoprotein and anti-Ro antibodies(9). Antiphospholipid antibodies and TP in SLE have been extensively studied in the past 30 years(10–15). The presence of aPL may increase the risk of TP in patients with SLE(12, 14, 15).

The therapeutic goals are to stop active bleeding, increase the PLT count and prevent future relapses. Urgent treatments include PLT transfusions, the administration of hemostatic intravenous immune globulin (IVIG), glucocorticoid pulse therapy and treatment with thrombopoietin receptor agonist. Long-term therapy is mainly based on glucocorticoids and immunosuppressors. As the administration of glucocorticoids and immunosuppressants may increase the risk of adverse effects, it is important to predict how patients will respond to the treatment, the potential benefit of glucocorticoid pulses and any adverse effects. However, we do not currently have a reliable method of predicting the therapeutic response in different people. Data from randomized trials are lacking, and the limited studies exploring the factors influencing the outcome in SLE-associated TP patients were mostly observational studies involving non-treatment-naïve patients.

Our study described the demographic features, clinical characteristics, laboratory findings and outcomes of a large series of treatment-naïve SLE patients with severe TP and explored the factors influencing prognosis in patients with SLE-associated TP. We found glucocorticoid pulses and immunoglobulin pulses were not beneficial for patients with SLE-associated TP. Demographic, clinical and laboratory characteristics are predictive for the prognosis. Therefore, immune and clinical phenotypes should be taken into consideration to realize individualized treatment.

Methods

Patient Population. This single-center retrospective study was approved by the Medical Ethics Committee of The First Affiliated Hospital of Zhengzhou University (Number: 2020-KY-255). It included treatment-naïve SLE patients complicated with severe TP who were admitted to our hospital from November 2010 to November 2018. In total, 5743 Chinese SLE patients fulfilled the 1997 SLE classification criteria revised by the American College of Rheumatology (ACR)(16), some of whom experienced several admissions. Of these patients, 1827 developed TP, and 690 developed severe TP. Those who had pseudothrombocytopenia, renal or liver dysfunction, or hematological disorders such as myelodysplastic syndrome, acute leukemia, aplastic anemia and thrombotic thrombocytopenic purpura; those who used

certain drugs that could cause thrombocytopenia; those with certain infections such as with hepatitis B virus (HBV), hepatitis C virus (HCV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV); and those who had been treated with glucocorticoids or immunosuppressants were excluded. To be included in the study, patients had to fulfill at least 4 of the 1997 ACR criteria for SLE, be at least 14 years old and be naïve to treatment with glucocorticoids, immunosuppressants or other treatments that could possibly affect the baseline values. TP was defined as a PLT count less than $100*10^9$/L, and severe TP was defined as a PLT count less than $30*10^9$/L. In total, 162 patients were included.

Data collection. In this retrospective study, demographic, clinical and laboratory data were collected between October 2019 and February 2020. Clinical manifestations, such as mucocutaneous lesions, arthritis, myositis, pleuritis, proteinuria and fever, were defined according to the SLE Disease Activity Index 2000 (SLEDAI-2K). Laboratory data included the PLT count, white blood cell count, hemoglobin level, complement component levels and autoantibodies. We recorded the therapy and the therapeutic response at week 1, week 4, week 24 and the endpoint. A total of 162 patients were analyzed.

Outcome and response to therapy. Response was defined as a PLT count $\geq 30 \times 10^9$/L: $30-49\times10^9$/L was considered a mild response, $50-100\times 10^9$/L was considered a moderate response, and $\geq 100 \times 10^9$/L was considered a complete response. Severe infection was defined as an infection that caused death or treatment in the hospital. Low-dose glucocorticoid complete response (LDG-CR) was defined as a complete response maintained for at least 12 weeks with a prednisone equivalent dose of no more than 7.5 mg.

Statistical methods. Qualitative variables are expressed as numbers and percentages, and quantitative variables are expressed as the medians and ranges or means ± standard deviations (SDs). We compared parameters between patients with and without a treatment response, with and without a complete response, and with and without serious infections, and between patients who did or did not die or achieve LDG-CR. Analyses were conducted using the SPSS 21.0 statistical package (SPSS, Chicago, USA). Variables with P values < 0.1 in the univariate analyses were further investigated using multivariate binary logistic regression analysis. Mortality was compared between the two groups using logistic regression and multivariate Cox regression, and the results were consistent. P values < 0.05 were considered to be statistically significant.

Results

Patients' characteristics. The median age at baseline was 31 years (range: 14– 80 years). The median disease duration was 1 month (range: 0- 240 months). The median duration of follow-up was 33 months (range: 0– 115 months). The detailed clinical characteristics and laboratory parameters of the patients are reported in Table 1 and Table 2.

Table 1
Characteristics of the quantitative data.

Item	Valid N	Missing N	Mean	S. E	Median	P_{25}	P_{75}
Age (years)	162	0	34.296	14.1271	31.00	24.75	42.25
Disease duration (months)	162	0	10.938	34.0045	1.00	0.00	6.00
PLT count	162	0	11.488	8.7108	8.50	4.00	18.00
SLEDAI-2K score	138	24	8.022	4.8698	7.00	5.00	11.00
Follow-up (months)	162	0	38.33	29.606	33.00	14.75	61.25

Table 2
Characteristics of the qualitative data.

Item	Yes(n (%))	No(n (%))	Missing value(n(%))
Sex (male)	17 (10.5)	145 (89.5)	
Mucocutaneous bleeding	102 (63.0)	60 (37.0)	
Visceral hemorrhage	9 (5.6)	153 (94.4)	
Mucocutaneous involvement	40 (24.7)	122 (75.3)	
Arthritis	40 (24.7)	122 (75.3)	
Raynaud's phenomenon	13 (8.0)	149 (92.0)	
Fever	45 (27.8)	117 (72.2)	
Proteinuria	23 (14.2)	139 (85.8)	
NPSLE	8 (4.9)	154 (95.1)	
PAH	6 (3.7)	129 (79.6)	27 (16.7)
Intestinal vasculitis	5 (3.1)	157 (96.9)	
Myositis	2 (1.2)	160 (98.8)	
Serositis	40 (24.7)	122 (75.3)	
Leukopenia	35 (21.6)	127 (78.4)	
Anemia	86 (53.1)	76 (46.9)	
Hypocomplementemia (C3)	100 (61.7)	38 (23.5)	24 (14.8)
Hypocomplementemia (C4)	57 (35.2)	81 (50.0)	24 (14.8)
ANA	162 (100)	0	
Anti-dsDNA	87 (53.7)	75 (46.3)	
Anti-Sm	46 (28.4)	115 (71.0)	1 (0.6)
Anti-nRNP	76 (46.9)	85 (52.5)	1 (0.6)
Anti-Nuc	57 (35.2)	104 (64.2)	1 (0.6)
Anti-Rib	43 (26.5)	118 (72.8)	1 (0.6)
Anti-His	47 (29.0)	114 (70.4)	1 (0.6)
a. Mucocutaneous involvement: rash, alopecia or mucosal ulcers;			
b. NPSLE: seizure, psychosis, organic brain syndrome, visual disturbance or cranial nerve disorder;			
c. PAH: pulmonary arterial pressure measured by ultrasound > 36 mmHg; anemia: Hb < 100 g/L.			

Item	Yes(n (%))	No(n (%))	Missing value(n(%))
Anti-SSA/Ro	91 (56.2)	70 (43.2)	1 (0.6)
Anti-SSB/La	19 (11.7)	142 (87.7)	1 (0.6)
GC pulses at week 1	25 (15.4)	137 (84.6)	
IgG pulses at week 1	18 (11.1)	144 (88.9)	
a. Mucocutaneous involvement: rash, alopecia or mucosal ulcers;			
b. NPSLE: seizure, psychosis, organic brain syndrome, visual disturbance or cranial nerve disorder;			
c. PAH: pulmonary arterial pressure measured by ultrasound > 36 mmHg; anemia: Hb < 100 g/L.			

Treatment response at week 1, week 4 and week 24. The treatment responses at three different times are displayed in Table 3, and the parallel program model is shown in Fig. 1. The response rates at week 1, week 2, and week 24 were 76.9%, 86.9%, and 91.2%, respectively, and the complete response rates were 35.9%, 75.9%, and 83.1%, respectively. We found that the rate of no response decreased as time went on, while the response and complete response rates increased.

Table 3
Treatment outcomes at three different points (N/%).

Time	NR	MR	MoR	CR	Death	Missing
Week 1	35 (21.6)	20 (12.3)	44 (27.2)	56 (34.6)	1 (0.6)	6 (3.7)
Week 4	16 (9.9)	3 (1.9)	13 (8)	110 (67.9)	3 (1.9)	17 (10.5)
Week 26	5 (3.1)	3 (1.9)	8 (4.9)	113 (69.8)	7 (4.3)	26 (16)

Serious infections, death and LDG-CR. Serious infection was defined as infection that caused death or needed treatment in the hospital. There were 21 patients who had concomitant serious infections during follow-up. There were 12 deaths in total, of which 4 were due to pulmonary infection, 1 was due to a pelvic infection attributed to abortion surgery, 2 was due to alveolar hemorrhage, 1 was due to severe acute pancreatitis, 1 was due to hepatic failure, 1 was due to cardiac failure, 1 was due to multiple organ failure, and 1 was due to acute abdomen. There were 93 patients who achieved LDG-CR, accounting for 67.4%. The above parameters are shown in Table 4.

Table 4
Serious infections, death and LDG-CR

Outcome	Yes	No	Missing (%)
Serious infection	21 (13.0)	121 (87.0)	
Death	12	150	
LDG-CR	93 (57.4)	45 (27.8)	24(14.8)
a. LDG-CR : Complete response with glucocorticoid that equals to no more than 7.5mg prednisone.			

Multivariate analysis of the risk factors. The significant results of multivariate analysis are shown in Table 5. Several factors, including baseline demographic features, clinical manifestations and autoantibodies, were associated with the outcome.

Table 5
Multivariate analysis

Time	Outcome	Risk factor	B	S.E.	Wald	Sig.	OR	95% CI
Week 1	R	male sex	-1.848	0.617	8.959	0.003	0.158	0.047–0.528
		age	-0.049	0.015	10.364	0.001	0.952	0.924–0.981
		serositis	*-0.884*	*0.453*	*3.799*	*0.051*	*0.413*	*0.170–1.005*
		anti-Sm	1.125	0.563	4.003	0.045	3.082	1.023–9.282
Week 1	CR	serositis	-1.123	0.495	5.155	0.023	0.325	0.123–0.858
Week 4	R	*visceral hemorrhage*	*-1.593*	*0.820*	*3.775*	*0.052*	*0.203*	*0.041–1.014*
		mucocutaneous involvement	*2.032*	*1.056*	*3.701*	*0.054*	*7.627*	*0.963–60.436*
Week 4	CR	age	-0.052	0.016	10.402	0.001	0.949	0.920–0.980
		anti-nRNP	1.418	0.455	9.708	0.002	4.128	1.692–10.071
		anti-SSB/La	2.219	1.074	4.268	0.039	9.194	1.120-75.445
Week 24	R	age	-0.084	0.031	7.411	0.006	0.920	0.866–0.977
		myositis	-3.493	1.609	4.715	0.030	0.030	0.001–0.712
		leukopenia	*-1.423*	*0.738*	*3.721*	*0.054*	*0.241*	*0.057–1.023*
		anti-SSA/Ro	-2.559	1.040	6.055	0.014	0.077	0.010–0.594

a. R: PLT > = 30*10^9/L;
b. CR: PLT > = 100*10^9/L;
c. LDG-CR: Complete response with glucocorticoid that equals to no more than 7.5mg prednisone.
d. The italicized variables marked with "*" were not statistically significantly associated with the outcome, but the P values were close to 0.05, and they could not be automatically eliminated by the software.

Time	Outcome	Risk factor	B	S.E.	Wald	Sig.	OR	95% CI
Week 24	**CR**	leukopenia	-1.382	0.523	6.998	0.008	0.251	0.090–0.699
		anti-SSA/Ro	-1.083	0.536	4.076	0.044	0.339	0.118–0.969
Follow-up	Serious infection	pulmonary arterial hypertension	1.955	0.859	5.178	0.023	7.062	1.311–38.037
	Death	myositis	3.178	1.486	4.574	0.032	24.000	1.304-441.709
		leukopenia	1.603	0.640	6.271	0.012	4.966	1.417–17.404
	LDG-CR	age	-0.044	0.015	8.065	0.005	0.957	0.929–0.987
		mucocutaneous hemorrhage	-0.920	0.438	4.418	0.036	0.399	0.169–0.940
		anti-nRNP	0.941	0.399	5.574	0.018	2.563	1.173–5.598

a. R: PLT > = 30*10^9/L;

b. CR: PLT > = 100*10^9/L;

c. LDG-CR: Complete response with glucocorticoid that equals to no more than 7.5mg prednisone.

d. The italicized variables marked with "*" were not statistically significantly associated with the outcome, but the P values were close to 0.05, and they could not be automatically eliminated by the software.

Effect of baseline demographic features. Male patients were relatively less likely to have a response at week 1 (OR = 0.158; 95% CI: 0.047–0.528; p = 0.003). Older patients were relatively less likely to have a response at week 1 (OR = 0.952; 95% CI: 0.924–0.981; p = 0.001), less likely to have a complete response at week 4 (OR = 0.949; 95% CI: 0.920–0.980; p = 0.001), less likely to have a response at week 26 (OR = 0.920; 95% CI: 0.866–0.977; p = 0.006), and less likely to achieve LDG-CR (OR = 0.957; 95% CI: 0.929–0.987; p = 0.005).

Effect of clinical features. Patients with serositis were relatively less likely to have a complete response or response at week 1 (OR = 0.325; 95% CI: 0.123–0.858; p = 0.023; and OR = 0.413; 95% CI: 0.170–1.005; p = 0.051), even though the latter was not statistically significant. Patients with myositis were relatively less likely to have a response at week 24 (OR = 0.030; 95% CI: 0.001–0.712; p = 0.030). Patients with leukocytopenia were relatively less likely to have a complete response at week 24 (OR = 0.251; 95% CI: 0.090–0.699; p = 0.008). At week 4, patients with visceral hemorrhage were relatively less likely to have a response, and patients with mucocutaneous involvement were relatively more likely to have a response

(OR = 0.203; 95% CI: 0.041–1.014; p = 0.052; and OR = 7.627; 95% CI: 0.963–60.436; p = 0.054), but the difference was not statistically significant. During follow-up, 21 patients had serious infections, and pulmonary arterial hypertension was the only risk factor for a serious infection (OR = 7.062; 95% CI: 1.311–38.037; p = 0.023). There were 12 deaths, and myositis and leukopenia were risk factors for mortality (OR = 24.000; 95% CI: 1.304–441.709; p = 0.032; and OR = 4.966; 95% CI: 1.417–17.404; p = 0.012). There were 93 patients who achieved LDG-CR, and patients with mucocutaneous hemorrhage were relatively less likely to achieve LDG-CR (OR = 0.399; 95% CI: 0.169–0.940; p = 0.036). The SLEDAI-2K score was not significantly associated with any outcome.

Effect of autoantibodies. Patients with anti-Sm antibodies were relatively more likely to have a response at week 1 (OR = 3.082; 95% CI: 1.023–9.282; p = 0.045). Patients with anti-nRNP antibodies or anti-SSB antibodies were relatively more likely to have a complete response at week 4 (OR = 4.128; 95% CI: 1.692–10.071; p = 0.002; and OR = 9.194; 95% CI: 1.120–75.445; p = 0.039). Patients with anti-Ro antibodies were relatively less likely to have a response or complete response at week 24 (OR = 0.077; 95% CI: 0.010–0.594; p = 0.014; and OR = 0.339; 95% CI: 0.118–0.969; p = 0.044). Patients with anti-nRNP antibodies were relatively more likely to achieve LDG-CR (OR = 2.563; 95% CI: 0.1173–5.598; p = 0.018).

Effect of glucocorticoid pulses and intravenous immunoglobulin pulses. There were 25 patients and 18 patients who were given glucocorticoid pulses and immunoglobulin pulses. However, neither glucocorticoid pulses nor immunoglobulin pulses were significantly associated with any outcome.

Discussion

In the past three decades, the pathogenesis and treatment of SLE-associated TP have been extensively studied. However, studies on the factors influencing the prognosis are relatively rare, and the few studies exploring the factors influencing treatment response in patients with SLE-associated TP have been mostly observational studies involving non-treatment-naïve patients. This is the first study to include a large number of treatment-naïve patients diagnosed with SLE-associated severe TP and explore the effects of demographic features, clinical manifestations, autoantibodies and treatment on outcomes at different points.

Our study showed that male sex was associated with not achieving a response at week 1 but not with other outcomes. Older age was associated with a poor response at week 1, week 4, and week 24 and with not achieving LDG-CR. Serositis was associated with not achieving a response at week 1. Myositis was associated not achieving a response at week 24. Leukocytopenia was associated with not achieving a complete response at week 24. Pulmonary arterial hypertension was a risk factor for serious infections. Myositis and leukopenia were risk factors for mortality. Mucocutaneous hemorrhage was associated with not achieving LDG-CR. Autoantibodies also affected the outcome. Anti-Sm antibodies were associated with a response at week 1. Anti-nRNP antibodies and anti-SSB antibodies were associated with a complete response at week 4. Moreover, anti-nRNP antibodies were associated with achieving LDG-CR.

Anti-Ro antibodies were associated with not achieving a response or a complete response at week 24. The findings above have not been reported before.

Baseline SLEDAI-2K scores, glucocorticoid pulses and immunoglobulin pulses at week 1 were not significantly associated with any outcome. Similarly, E J ter Borg et al. reported that intravenous gammaglobulin was of limited value in the treatment of SLE-associated TP(17), although intravenous immunoglobulin has been reported to be effective for the treatment of SLE-associated TP in case series(18, 19).

This study has some limitations. First, the data were collected retrospectively, the follow-up period varied greatly, and some of the data was incomplete. Second, as this was a single-center study, selection bias was inevitable. Third, although we recorded the presence of antiphospholipid antibodies (aPLs) and bone marrow megakaryocytes, the parameters were not included in the analysis, as the proportions of missing values exceeded 20%. Lidan Zhao et al. found that low bone marrow megakaryocyte counts predicted a poor therapeutic response of severe TP in patients with SLE(20). Besides, although all patients accepted systemic glucocorticoids as initial treatment, their subsequent options were different, most receiving hydroxychloroquine and immunosuppressants as additions to glucocorticoids and others not.

Conclusions

In patients with SLE-associated TP, male sex, older age, serositis, myositis, leukocytopenia and anti-Ro antibodies are predictive of a poor response. Anti-Sm antibodies, anti-nRNP antibodies and anti-SSB antibodies are predictive of a positive response. Older age and mucocutaneous hemorrhage predict the failure to achieve LDG-CR. Anti-nRNP antibodies predict the achievement of LDG-CR. Pulmonary arterial hypertension is associated with serious infections. Myositis and leukopenia are correlated with death. Early glucocorticoid pulses and immunoglobulin pulses do not improve outcomes.

This study may give us some tips in clinical practice and help realize individualized treatment for patients with SLE-associated TP. Glucocorticoid pulses and immunoglobulin pulses are not recommended because they do not benefit the patients. Patients with pulmonary arterial hypertension may need prophylactic anti-infection therapies. Patients with myositis and leukopenia should be followed up more intensively.

Abbreviations

TP
thrombocytopenia
SLE
systemic lupus erythematosus
LDG-CR
low-dose glucocorticoid complete response

PLT
platelet
aPL
antiphospholipid antibodies
IVIG
intravenous immune globulin
SLEDAI-2K
SLE Disease Activity Index 2000
R
response
MR
mild response
MoR
moderate response
CR
complete response

Declarations

Ethics approval and consent to participate: This single-center retrospective study was approved by the Medical Ethics Committee of The First Affiliated Hospital of Zhengzhou University (Number: 2020-KY-255).

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

Authors' contributions: LJL, SYL and TFL have made substantial contributions to the design of the work, as well as interpretation of data. LJL, WL and JML have drafted the work. LJL, CW, YLZ and LZ have done a lot in the acquisition of the data. CW, XJL and JLS have analyzed the data. TFL and YJH have revised the work.

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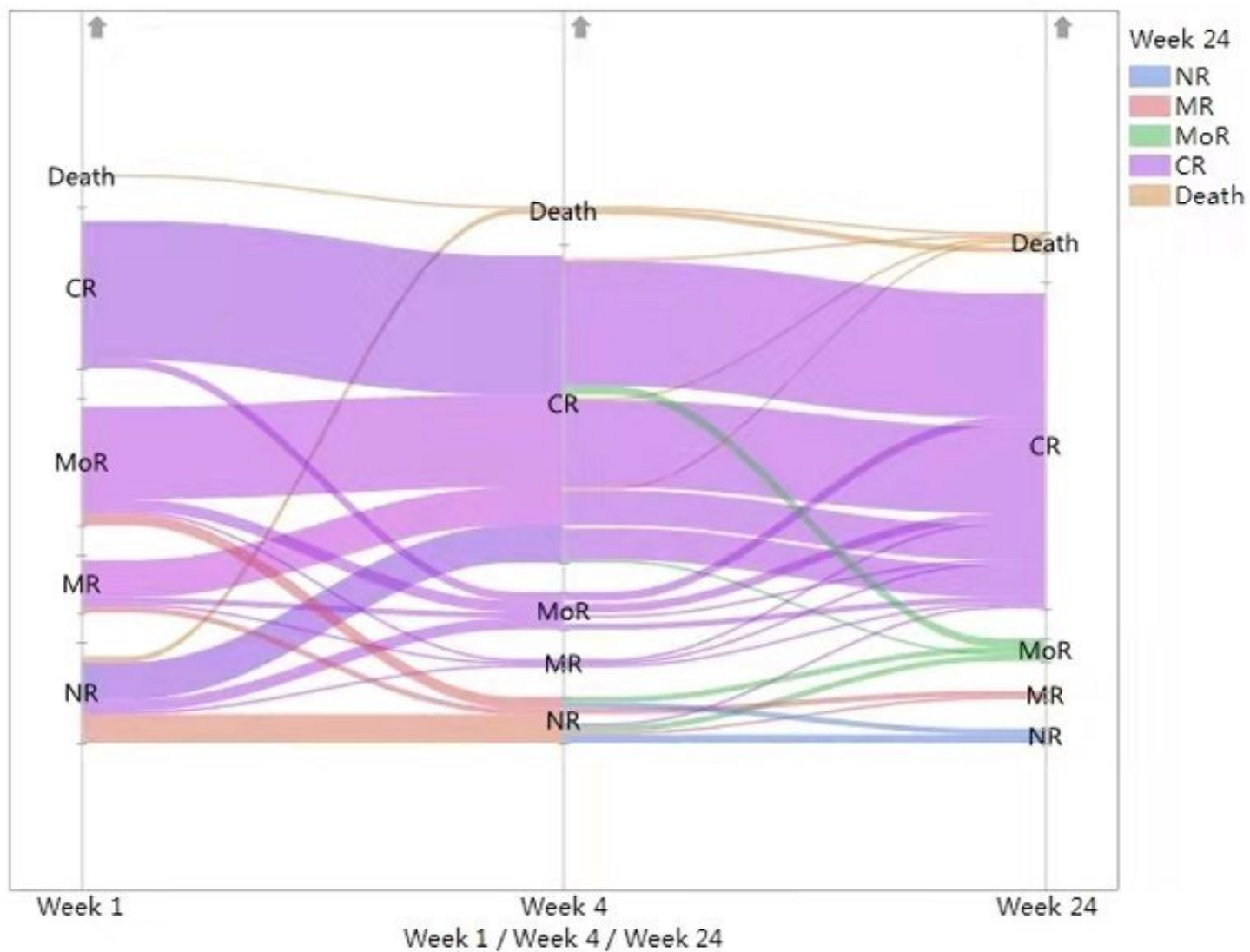
Figures

Figure 1

Parallel program of the outcome at three points