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ORIGINAL RESEARCH

IgG-Associated Hypocomplementemia in Neonatal Lupus: A Retrospective Multicenter Study

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Background: Hypocomplementemia, defined as a complement C3 or C4 level below the normal lower limit, is strongly associated with an unfavorable prognosis in patients with autoimmune diseases. This study aimed to explore the clinical features and outcomes of patients with neonatal systemic lupus erythematosus (NLE) with hypocomplementemia.

Methods: This retrospective clinical study was conducted across four tertiary hospitals in Eastern China on January 1, 2011, and December 31, 2023. This study included 91 patients with NLE. Patients were classified into hypocomplementemic and non-hypocomplementemic groups according to their serum C3 and/or C4 levels. Risk factors for the development of hypocomplementemia were explored using univariate/multifactorial analyses, organ involvement, and follow-up outcomes were compared between groups.

Results: The number of NLE patients with hypocomplementemia was 36 (39.56%). Hypocomplementemia group had a significantly lower proportion of fish oil supplementation during pregnancy, a higher proportion of cesarean deliveries, mothers with systemic lupus erythematosus, double antibody positivity for anti-SSA and anti-SSB, and higher serum IgG levels. Multivariate analyses showed that maternal allergic diseases, double antibody positivity, and serum IgG levels were risk factors for hypocomplementemia. Baseline IgG levels negatively correlated with complement C3 and C4 levels. NLE Patients with hypocomplementemia are more likely to have thrombocytopenia, hypoproteinemia, or gastrointestinal involvement than those without hypocomplementemia. Systemic application of glucocorticoids was significantly more prevalent in the hypocomplementemia group. Long-term follow-up revealed that allergy-associated disorders were common in patients with NLE and hypocomplementemia, followed by developmental delay, severe infections, attention- deficit hyperactivity disorder, and anxiety/depression, respectively. Log-rank analysis revealed that these patients had significantly higher frequencies of allergic diseases and developmental delays later in life.

Conclusion: Maternal allergic diseases, double antibody positivity, and serum IgG levels were associated with the development of hypocomplementemia in children with NLE. Patients with hypocomplementemia-associated NLE typically exhibit a more severe disease course.

Keywords: lupus erythematosus, neonate, immunoglobulin G, hypocomplementemia, risk factors, prognosis

Introduction

Neonatal lupus erythematosus (NLE) is a syndrome characterized by multi-organ damage in the fetus or newborn due to the transfer of maternal IgG antibodies across the placenta.[1,2] Increased expression of transplacentally acquired maternal autoantibodies, mostly anti-sjogren's syndrome antigen A(anti-SSA) and/or anti-sjogren's syndrome antigen B(anti-SSB) antibodies -induced inflammation, apoptosis, fibrosis, and type I interferon (IFN) is believed to contribute to NLE development.[3,4] Transplacentally acquired maternal autoantibodies promote the formation of antigen-antibody complexes

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in the fetus, which further leads to organ damage, and this process promotes the activation of complement-mediated classical and bypass pathways, resulting in a decrease in complement levels in the serum.[5,6]

Hypocomplementemia is defined as a complement C3 or C4 level below the normal lower limit. Numerous studies have confirmed that patients with autoimmune diseases (AD) are more prone to hypocomplementemia, which is closely linked to disease activity, severity, and prognosis.[7–9] Our previous studies have found that the incidence of hypocomplementemia in patients with NLE was significantly higher than in the general population.[10] We hypothesized that hypocomplementemia would be strongly associated with the clinical features and prognosis of patients with NLE. However, the clinical characteristics and prognoses of patients with NLE, with or without hypocomplementemia, have not yet been reported. Therefore, this study aimed to compare the clinical characteristics and prognostic outcomes of patients with NLE with and without hypocomplementemia to identify the risk factors for hypocomplementemia development in patients with NLE and the clinical outcomes of these children.

Methods

Study Subjects

This was a multicenter, retrospective clinical study. The study subjects were children with NLE admitted to the Children's Hospital of Soochow University, Yangzhou Maternal and Child Health Hospital, Affiliated Suzhou Hospital of Nanjing Medical University, and Huai'an Maternal and Child Health Hospital on January 1, 2011, and December 31, 2023, respectively. The study was approved by the Ethics Committee of all Hospital (No. 2023CS024). Written informed consent was obtained from the guardians of all patients. All methods were performed in accordance with the ethical standards as laid down in the Declaration of Helsinki and its later amendments or comparable ethical standards.

Children were divided into hypocomplementemia and non-hypocomplementemia groups based on whether they had combined hypocomplementemia. Risk factors for the development of hypocomplementemia were further explored, and organ involvement and outcomes were compared between the two groups.

Exclusion

(1) Significant deficiencies in the clinical data that could bias the results. (2) Patients who refused to participate in the clinical study.

Diagnosis and Definitions

The diagnosis of NLE is based on a pregnant woman or newborn with AD exhibiting clinical features associated with NLE and seropositive.[11] Hypocomplementemia is defined as complement C3 or C4 levels below the lower limit of normal. Severe infections are defined as those that required hospitalization for infectious diseases. Children's development was assessed using the Gesell Developmental Scale, which includes five domains: gross motor, fine motor, language, individual-social, and adaptive behaviors. Attention deficit hyperactivity disorder (ADHD), anxiety, depression, and Tourette syndrome (TS) met the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5).[12] Allergic diseases include food allergy, atopic dermatitis, current wheezing, asthma, allergic rhinitis, etc.[13] The diagnosis of AD in children follows the relevant definitions and diagnostic criteria in Zhufutang Practical Paediatrics.[14]

Data Collection and Follow-up

Data were extracted by reviewing inpatient and outpatient electronic case records, and the study included both telephone and offline follow-up visits. Electronic case data collection included the history of AD in the pregnant woman, parental history of allergic diseases, demographic characteristics, clinical presentation, and laboratory and imaging tests. The demographic characteristics included sex, gestational age, and birth weight. Laboratory investigations included routine blood, biochemical, and serological tests for AD. Imaging tests included ultrasonography, echocardiography, computed tomography (CT), and magnetic resonance imaging (MRI). Main treatment during hospitalization included antibiotics, platelet, leukocyte-reduced suspended red blood cells, intravenous immunoglobulin, and systemic application of glucocorticoids. Other tests included video/dynamic EEG and the Gesell Assessment Scale. Patient development, ADHD,

anxiety/depression, allergic diseases, and other associated conditions were assessed by researchers and specialists in child health and rheumatology. All evaluators received relevant theoretical and practical training before the start of the study.

Statistical Analysis

Descriptive statistics were presented as mean ± SD or median (P25, P75) for continuous variables and frequency (percentage) for categorical variables. The chi-square test was used for categorical variables, and the non-parametric Mann–Whitney *U*-test was used for continuous variables. Risk factors differentiating between the two groups were analyzed using binary logistic regression. Spearman correlation was used to analyze the relationship between C3/C4 and serum IgG levels. Finally, differences in allergic diseases and developmental delay (DD) between the two groups were compared using the Kaplan-Meier method. Data were analyzed using R (version 4.2.1), and the results were visualized using ggplot2. A p-value of $p<0.05$ was considered statistically significant.

Results

Clinical Features of Patients With NLE With Hypocomplementemia

A flowchart of the study is provided in Figure 1. A total of 102 patients with NLE were admitted between January 1, 2011, and December 31, 2023. Eleven patients with incomplete clinical data and those who refused to participate were excluded, and 91 patients were ultimately enrolled. The mean gestational age of the patients was 37 + 2 weeks (36+1, 38 +4), and the mean birth weight was 2510.35 g (1960.20, 3104.30). A total of 36 (39.56%) patients were included in the hypocomplementemia group.

A comparison of the clinical characteristics of the two patient groups is presented in Table 1. Compared to the non-hypocomplementemic group, the hypocomplementemic group had a significantly lower proportion of mothers with fish oil supplementation during pregnancy, a higher proportion of cesarean deliveries, mothers with SLE, double antibody positivity for anti-SSA and anti-SSB, and higher serum IgG levels ($P<0.05$) (Figure 2A). There were no significant differences between the two groups in terms of sex, gestational age, birth weight, parental history of allergic diseases, maternal AD other than SLE, micronutrient preparations and probiotic supplementation, environmental exposure to smoke, history of pet exposure, anti-SSA, anti-SSB, anti-U1-ribonucleic protein (anti-U1-RNP), triple antibody positivity to anti-SSA, anti-SSB, U1-RNP, serum IgM, eosinophil count, or C-reactive protein (CRP) levels ($P>0.05$).

Risk factors for hypocomplementemia were analyzed, and are shown in Table 2. Logistic regression analyses were performed for variables that differed significantly between the two groups. Multivariate analyses showed that maternal

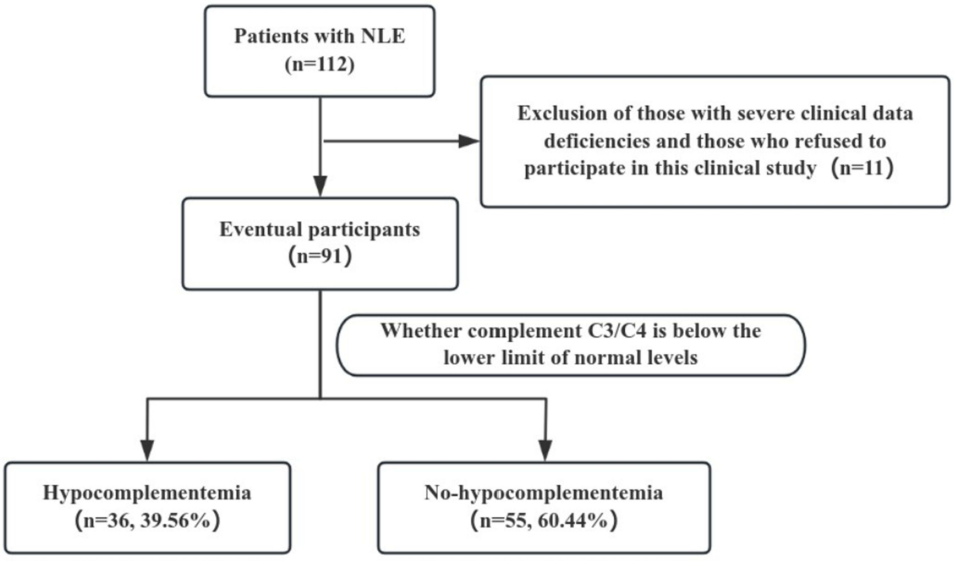

Figure 1 Flow chart of the study population. NLE, neonatal lupus erythematosus.

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Table 1 Clinical Features of NLE Patients With Hypocomplementemia

Parameters	NLE (n=91)	Hypo (n=36)	No-hypo (n=55)	*P*
Baseline characteristics				
Sex				
Male	37 (40.66)	14 (38.89)	23 (41.82)	0.781
Female	54 (59.34)	22 (61.11)	32 (58.18)	
Gestational age (weeks)	37+2 (36+1, 38+4)	36+5 (35+4, 38+2)	37+5 (36+4, 39+1)	0.279
Birth weight (g)	2510.35 (1960.20, 3104.30)	2480.50 (1890.50, 3058.40)	2590.10 (2150.45, 3270.60)	0.233
Mode of delivery				
Cesarean section	40 (43.96)	21 (58.33)	19 (34.55)	0.025
Vaginal delivery	51 (56.04)	15 (41.67)	36 (65.45)	
Prenatal factors				
Maternal allergic disease	38 (41.75)	20 (55.55)	18 (32.73)	0.031
Father's allergic disease	17 (18.68)	7 (16.67)	10 (20.00)	0.880
Maternal autoimmune diseases				
Systemic lupus erythematosus	51 (56.04)	26 (72.22)	25 (45.45)	0.037
Photosensitivity symptoms	10 (10.99)	3 (8.33)	7 (12.73)	0.755
Mixed connective tissue disease	4 (4.40)	1 (2.78)	3 (5.45)	0.931
Sjogren's syndrome	8 (8.79)	1 (2.78)	5 (9.09)	0.450
Autoantibody abnormalities	9 (9.89)	2 (5.56)	5 (9.09)	0.829
—	13 (14.29)	4 (11.11)	9 (16.36)	0.694
Lupus activity during pregnancy	7 (7.69)	3 (8.33)	4 (7.27)	1.000
Trace element	52 (57.14)	21 (58.33)	31 (56.36)	0.853
Fish oil	49 (53.85)	24 (66.67)	25 (45.45)	0.047
Probiotics	31 (34.07)	13 (36.11)	18 (32.73)	0.739
Exposure to smoky environments	27 (29.67)	11 (30.56)	16 (29.09)	0.881
Pet exposure during pregnancy	23 (25.27)	8 (22.22)	15 (27.27)	0.588
Serological indicators				
Anti-SSA	68 (74.73)	29 (80.56)	39 (70.91)	0.300
Anti-SSB	47 (51.65)	23 (63.89)	24 (43.64)	0.059
Anti-U1-RNP	23 (25.27)	9 (28.00)	14 (25.45)	0.961
Anti-SSA, Anti-SSB	41 (45.05)	21 (58.33)	20 (36.36)	0.039
Anti-SSA, Anti-SSB, U1-RNP	11 (12.09)	4 (11.11)	7 (12.73)	1.000
IgG (g/L)		23.65 (19.00, 26.08)	20.00 (16.50, 22.65)	0.007
IgM (mg/L)		323.05 (279.36, 445.14)	315.87 (275.89, 441.02)	0.642
Eosinophil count ($\times 10^9$/L)		0.14 (0.07, 0.23)	0.12 (0.03, 0.20)	0.094
C-reactive protein (mg/L)		0.16 (0.06, 0.79)	0.14 (0.02, 0.68)	0.753

Abbreviations: NLE, Neonatal lupus erythematosus; Hypo, hypocomplementemia.

allergic diseases, anti-SSA and-SSB double antibody positivity, and serum IgG levels were risk factors for the development of hypocomplementemia in patients with NLE.

Correlation of Complement C3, C4 and Serum IgG Levels

The correlation between complement C3 and C4 levels and serum IgG levels is presented in Figure 2B and C. Complement C3 levels were positively correlated with C4 levels (r = 0.813, $p < 0.001$) (Figure 2B). C3 levels were

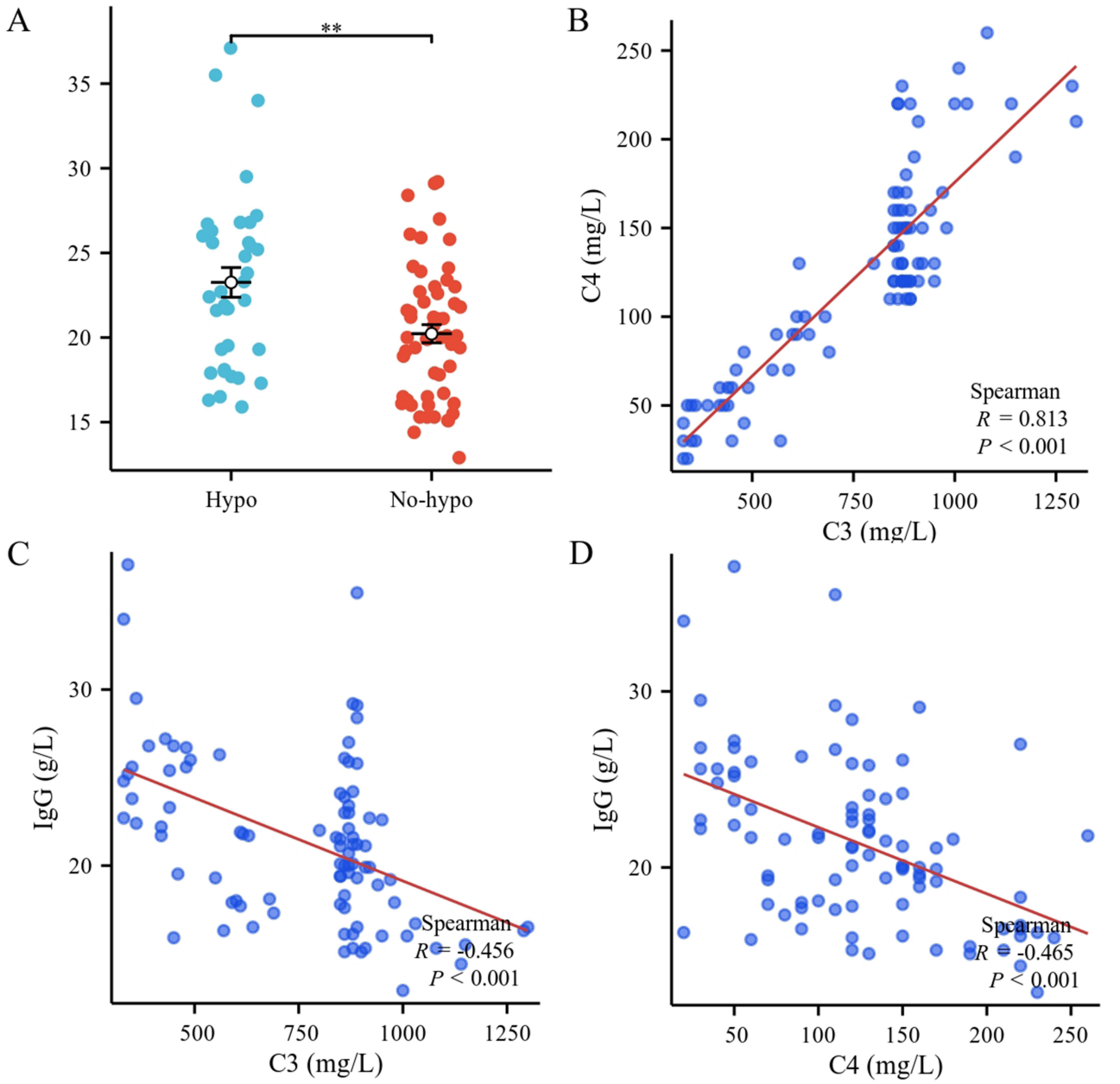

Figure 2 IgG levels and their correlation with complement C3/C4. (**A**) IgG levels were significantly higher in the hypocomplementemia (Hypo) group than in the no-hypocomplementemia (No-hypo) group (**B**) C4 levels positively correlated with C3. (**C**) C3 levels negatively correlated with igG. (**D**) C4 levels negatively correlated with igG. ***P<0.01*.

negatively correlated with IgG levels (r = −0.456, $p < 0.001$) (Figure 2C). C4 levels were negatively correlated with IgG levels (r = −0.465, $p < 0.001$) (Figure 2D).

Organ Involvement in Patients With NLE With Hypocomplementemia

Organ involvement in patients with NLE is presented in Table 3. Organ involvement in NLE patients with hypocomplementemia were mainly manifested as cutaneous involvement (83.33%), gastrointestinal (80.56%), hematological (72.22%), cardiac (50.00%) and neurological involvement (27.78%). Among the various types of hematological involvement, anemia was the most common (55.56%), followed by thrombocytopenia (52.78%), neutropenia (44.44%), hypoproteinemia (27.78%), and coagulation abnormalities (19.44%).

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Table 2 Analysis of Risk Factors for the NLE Patients With Hypocomplementemia

Characteristics	OR	95% CI	*P*
Cesarean section	1.570	0.513–4.812	0.430
Maternal allergic diseases	2.968	1.631–6.379	0.026
Maternal SLE	2.077	0.746–5.781	0.162
Fish oil	1.299	0.461–3.658	0.621
Anti-SSA, Anti-SSB	2.453	1.096–6.031	0.032
Serum IgG levels	1.007	1.002–1.012	0.008

Abbreviations: NLE, neonatal lupus erythematosus; SLE, systemic lupus erythematosus.

Table 3 Organ Involvement, Main Treatments and Long-Term Outcome in NLE Patients With Hypocomplementemia

Parameters	NLE (n=91)	Hypo (n=36)	No-hypo (n=55)	*P*
Organ involvement				
Cutaneous (rash)	79 (86.81)	30 (83.33)	49 (89.09)	0.427
Hematological				
Total	63 (69.23)	26 (72.22)	37 (67.27)	0.617
Anemia	49 (53.85)	20 (55.56)	29 (52.73)	0.691
Neutropenia/deficiency	30 (32.97)	16 (44.44)	14 (25.45)	0.060
Thrombocytopenia	36 (39.56)	19 (52.78)	17 (30.91)	0.037
Coagulation abnormalities	18 (19.78)	7 (19.44)	11 (20.00)	0.948
Hypoproteinemia	16 (17.58)	10 (27.78)	6 (10.91)	0.039
Cardiac				
Total	47 (51.65)	18 (50.00)	29 (52.73)	0.799
Congenital heart block	15 (16.48)	6 (16.67)	9 (16.36)	0.970
Structural cardiac abnormalities	38 (41.76)	15 (41.67)	23 (41.82)	0.989
Gastrointestinal	60 (65.93)	29 (80.56)	31 (56.36)	0.017
Neurological	26 (28.57)	10 (27.78)	16 (29.09)	0.892
Main treatments during hospitalization				
Antibiotics	46 (50.55)	17 (47.22)	29 (52.73)	0.608
Platelet	20 (21.98)	10 (27.78)	10 (18.18)	0.280
Leukocyte-reduced suspended red blood cells	35 (38.46)	11 (30.56)	14 (25.45)	0.594
Intravenous immunoglobulin	36 (39.56)	16 (44.44)	20 (36.36)	0.441
Systemic application of glucocorticoids	49 (53.85)	24 (66.67)	25 (45.45)	0.047
Long-term follow-up				
Severe infection	25 (29.67)	12 (33.33)	13 (23.64)	0.311
Allergic diseases	35 (38.46)	19 (52.78)	16 (29.09)	0.023
Attention deficit hyperactivity disorder	13 (14.29)	5 (13.89)	7 (12.73)	0.872
Anxiety/depression	6 (6.59)	2 (5.56)	4 (7.27)	1.000
Tourette syndrome	2 (2.20)	0 (0.00)	2 (3.64)	0.670
Developmental delay	22 (24.18)	13 (36.11)	9 (16.36)	0.031
Autoimmune disease	2 (2.20)	1 (2.78)	1 (1.82)	1.000

Abbreviations: NLE, Neonatal lupus erythematosus; Hypo, hypocomplementemia.

Compared to non-hypocomplementemic patients, those in the hypocomplementemic group were more likely to have thrombocytopenia (19 [52.78%] vs 17 [30.91%], $p < 0.05$), hypoproteinemia (10 [27.78%] vs 6 [10.91%], $p < 0.05$), and gastrointestinal involvement (29 [80.56%] VS 31 [56.36%], $p < 0.05$).

Main Treatment During Hospitalization in Patients With NLE With Hypocomplementemia

Main treatment during hospitalization of patients with NLE is presented in Table 3. Systemic application of glucocorticoids was significantly more prevalent in the hypocomplementemia group compared to the non-hypocomplementemia group ($p < 0.05$). No significant differences were observed between the two groups regarding the use of antibiotics, platelets, leukocyte-reduced suspended red blood cells, and intravenous immunoglobulin ($p > 0.05$).

Long-Term Follow-up of Patients With NLE With Hypocomplementemia

The long-term follow-up of patients with NLE is presented in Table 3, Figure 3A and B. Long-term outcomes in NLE patients with hypocomplementemia were mainly manifested as allergic diseases (52.78%), followed by DD (36.11%), severe infections (33.33%), ADHD (13.89%), anxiety/depression (5.56%), and AD (2.78%). Compared to non-hypocomplementemic patients, those with hypocomplementemia were more likely to have allergic diseases (19 [52.78%] vs 16 [29.09%], $p < 0.05$) and DD (13 [36.11%] vs 9 [16.36%], $p < 0.05$). There was no significant difference between the two groups in the incidence of severe infections (12 [33.33%] vs 13 [23.64%]), ADHD (5 [13.89%] vs 7 [12.73%]), anxiety/depression (2 [5.56%] vs 4 [7.27%]), TS (0 [0.00%] vs 2 [3.64%]) and AD (1 [2.78%] vs 1 [1.82%]) did not differ significantly in their occurrence ($p > 0.05$). The Kaplan-Meier analysis of the occurrence of allergic diseases and DD in patients with NLE and hypocomplementemia is presented in Figure 3C and D. The Log rank test showed that patients with hypocomplementemia had a significantly higher risk of developing DD and allergic diseases than those without hypocomplementemia ($P < 0.05$).

Discussion

This study included four tertiary hospitals in East China to analyze the clinical characteristics and follow-up outcomes of NLE with hypocomplementemia. Maternal allergic diseases, double-antibody positivity, and serum IgG levels were identified as risk factors for the development of hypocomplementemia in patients with NLE. Additionally, patients with NLE with hypocomplementemia were more likely to have thrombocytopenia, hypoproteinemia, and gastrointestinal involvement, with a significantly higher frequency of allergic diseases and DD in the long term compared to those without hypocomplementemia. These findings suggest that patients with NLE and hypocomplementemia have a more severe disease course and are more likely to experience adverse long-term outcomes.

The etiopathogenesis of hypocomplementemia in patients with NLE: Previous studies have shown that conditions such as bacterial infections, AD, and malignant tumors can significantly deplete complement components, leading to hypocomplementemia.[15–17] Hyperactivation of the complement system is often observed in AD.[18] In this study, maternal allergic diseases, the percentage of anti-SSA and anti-SSB double antibody positivity, and increased serum IgG levels were identified as risk factors for the development of hypocomplementemia in patients with NLE, and both complement C3/C4 and serum IgG levels were negatively correlated. The primary mechanism for the development of NLE involves maternal IgG antibodies acting on the fetus via the placenta, suggesting that hypocomplementemia in patients with NLE may be associated with an increase in serum IgG levels, which has been demonstrated in IgG4-related disorders.[8] Human IgG is classified as IgG1-4, of which IgG1-3 activate the complement system, with elevated serum IgG1 concentrations directly correlating with reduced C3 and C4 levels.[17,19,20]

Overactivation of the complement cascade leads to the production of inflammatory mediators and chemokines, resulting in organ damage. Decreased complement C3 and C4 levels often indicate of severe disease in patients with AD or concurrent organ damage.[21] In this study, patients with NLE and hypocomplementemia were more likely to have thrombocytopenia, hypoproteinemia, and gastrointestinal involvement. The core mechanism of NLE involves multi-organ damage caused by the transfer of the maternal IgG antibodies through the placenta to the fetus. IgG-coated

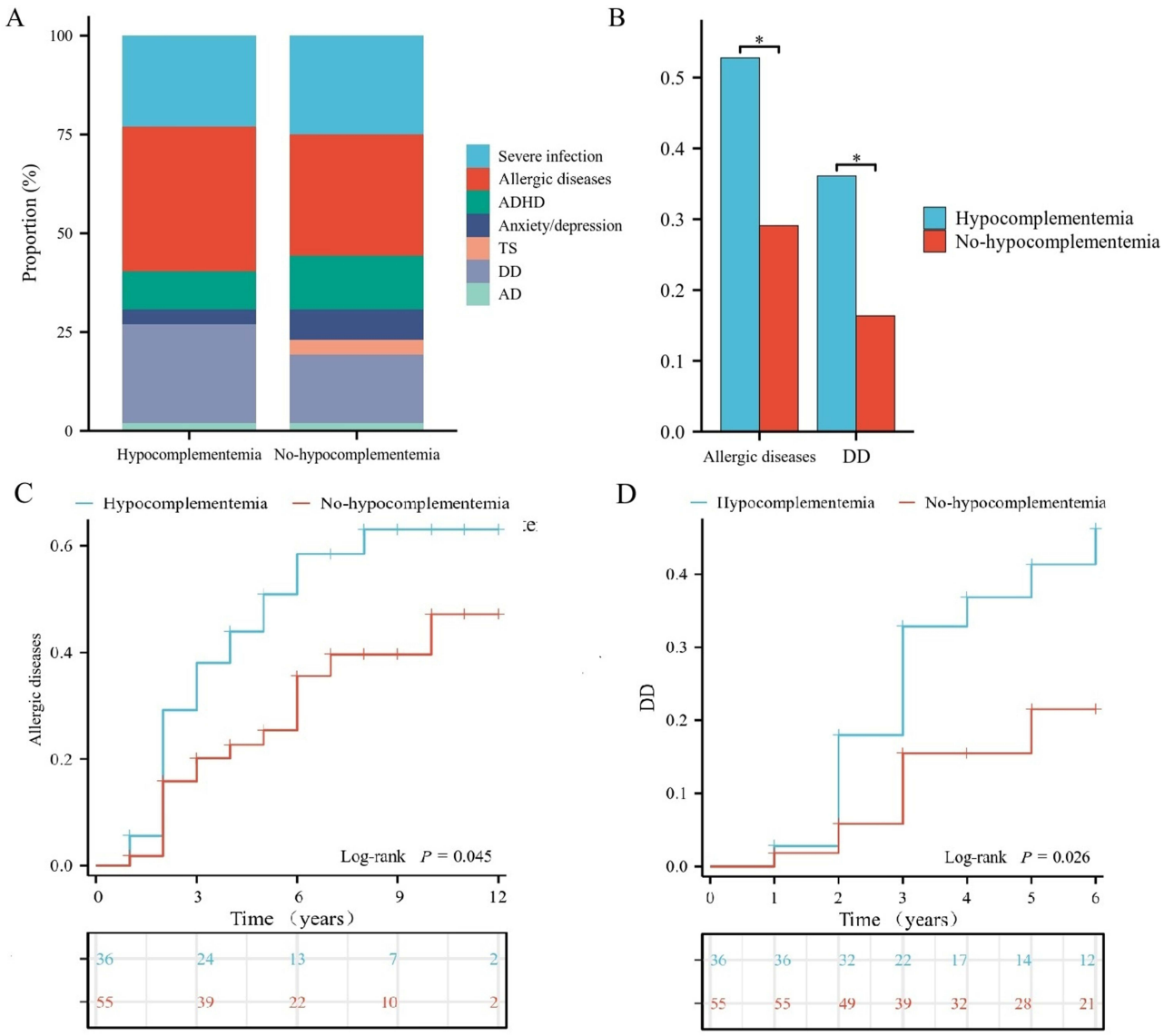

Figure 3 Follow-up of the study population. (**A**) Distribution of long-term prognosis of patients in the two groups. (**B**) Comparison of allergic diseases and DD in two groups. (**C**) Kaplan–Meier analysis of the occurrence of allergic diseases in the two groups. (**D**) Kaplan–Meier analysis of the occurrence of DD in the two groups. *$P<0.05$. **Abbreviations**: ADHD, attention deficit hyperactivity disorder; TS, Tourette syndrome; DD, developmental delay; AD, autoimmune disease.

platelets initiate complement activation via the classical pathway, leading to platelet destruction and enhanced clearance by C3b-coated platelets.[22] In our study, Serum IgG levels were significantly higher in the patients with hypocomplementemia than in those without. However, there is no direct evidence to confirm the correlation between thrombocytopenia and serum IgG levels in NLE patients, and further basic studies are needed to verify it. In patients with AD, high serum IgG and low complement levels often indicate a strong immune-inflammatory response, and neonates with immature gastrointestinal barriers and rich intestinal mucosal vasculature are more susceptible to antibody-mediated damage.[23] This may explain the higher incidence of gastrointestinal involvement in patients with NLE and hypocomplementemia, leading to an increased incidence of hypoproteinemia. In addition, in our study, the rate of systemic application of glucocorticoids in NLE patients with hypocomplementemia was significantly higher, which also suggests that such children may have a more severe inflammatory response. Glucocorticoids exhibit significant sensitivity towards fetuses and newborns, exerting prolonged influences on their growth, development, and immune homeostasis.[24,25] Nevertheless, the association between glucocorticoid exposure and the long-term adverse prognosis in children with NLE requires further investigation.

The complement system is essential for innate immunity and the amplification cascade it triggers, which not only protects the body against pathogens but also plays a role in various physiological functions, recently linked to autoimmune and neuropsychiatric disorders.[26–29] Patients with AD have a significantly higher prevalence of infectious, allergic, autoimmune, and developmental diseases. In this study, the occurrence of allergic diseases and DD was significantly higher in the hypocomplementemia group than in the non-hypocomplementemia group. Complement levels directly impact the host immune status, which may contribute to the development of allergic processes and the high incidence of allergic diseases in patients with NLE and hypocomplementemia.[30,31] Studies on neonatal hypocomplementemia, growth, and development are relatively rare. Numerous preclinical studies and human biopsies have shown that complement system activation is central to the inflammatory and anti-inflammatory response in the central nervous system, involving a complex interplay among astrocytes, microglia, and neuronal synaptic networks.[32,33] This may explain why the incidence of DD in patients with NLE and hypocomplementemia is significantly higher than that in the non-hypocomplementemic group, although the specific mechanism requires further investigation.

The treatment of some patients with NLE involves systemic administration of steroids, and hemodialysis is often considered for those with more severe or recurrent disease.[34] However, hemodialysis is an invasive procedure that can significantly impact circulation and is associated with a higher risk of complications. Recent studies have shown that complement receptor inhibitors are effective in treating PNH- and ANCA-related vasculitis.[22,35] Therapeutic modulation of complement proteins may be beneficial for patients with severe NLE; however, the underlying mechanisms by which complement contributes to NLE development need further clarification.

This is first to investigate the risk factors for hypocomplementemia in patients with NLE and report the associated clinical features and outcomes, which have not been previously described. However, there are several limitations to this study. First, this was a retrospective study, and relevant laboratory tests were not performed consistently over time. Second, parental disease diagnoses in this study only included allergic diseases that were definitively diagnosed by specialized healthcare providers. Third, organ involvement in patients with NLE is transient, and some patients with less severe disease may not have been hospitalized, potentially leading to bias.

In conclusion, our study suggests that maternal allergic diseases, double antibody positivity, and serum IgG levels may be associated with hypocomplementemia in patients with NLE, who typically experience a more severe course.

Data Sharing Statement

The data underlying this article are available in the article.

Ethical Approval

The study was approved by the Ethics Committee of all Hospital (No. 2023CS024). Written informed consent was obtained from the guardians of all patients. All methods were performed in accordance with the ethical standards as laid down in the Declaration of Helsinki and its later amendments or comparable ethical standards.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. The overall figures remained the property/copyright of all authors.

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Disclosure

The authors declare that they have no conflicts of interest.

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