Clinical characteristics and outcome of IgG4-related disease with hypocomplementemia: a prospective cohort study

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Abstract

Background

Immunoglobulin G4 related disease (IgG4-RD) is a newly recognized systemic, immune-mediated and fibro-inflammatory disease. Hypocomplementemia was found in part of IgG4-RD patients especially in the setting of active disease.

Objectives

This study aimed to clarify the clinical features, treatment efficacy and outcome in IgG4-RD patients with hypocomplementemia.

Methods

312 IgG4-RD patients were recruited in our prospective cohort conducted in Peking union medical college hospital. Patient's demographic data, clinical characteristics, laboratory parameters, treatment and outcome were analyzed.

Results

Hypocomplementemia was identified in 65(20.8%) cases of untreated IgG4-RD patients at baseline. The average age of hypocomplementemia group was 55.85±10.89 years, with male predominance (72.3%). Compared with normal complement group, patients with hypocomplementemia were likely to have more involved organs,higher IgG4-RD responder index (IgG4-RD RI), higher laboratory parameters such as counts of eosinophils, inflammatory markers□immunoglobulin G(IgG), IgG1, IgG3, IgG4 and IgE. In addition, lymph nodes, lacrimal gland□submandibular gland□parotid gland□paranasal sinus□bile ducts and prostate gland were more commonly affected($p < 0.05$). Serum C3 and C4 were negatively correlated with the number of involved organs, IgG4-RD RI, hypersensitive C-reactive protein (hsCRP), IgG, IgG1, IgG3 and IgG4. 64(98.5%) patients responded quickly to initial therapy at 3-month follow-up. Fifteen (23.1%) patients relapsed during follow-up with mean recurrence time of 14.2±13.8 months. Compared with normal complement group, there was no significant difference of relapse rate in two groups ($P = 0.7559$).

Conclusions

Clinical characteristics of IgG4-related disease with hypocomplementemia differs from normal complement group.Serum C3 and C4 at baseline before treatment could be biological markers for disease activity. IgG4-RD with hypocomplementemia responded well to treatment and had no significant difference of relapse rate in IgG4-RD with normal complement.

Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a newly recognized multi-organ, immune-mediated and fibro-inflammatory disease with pathologically characterized by IgG4-positive lymphoplasmacytic infiltration, storiform-fibrosis and obliterative phlebitis. IgG4-RD affects nearly every organ, particularly lacrimal glands, salivary glands, pancreas, bile ducts, lungs, kidneys, retroperitoneum, artery, thyroid gland, meninges and orbits. Approximately a quarter to a third of patients with active IgG4-RD have hypocomplementemia defined by the low level of complement component C3 or C4 [1.2].

Complement is one of the first lines of defense against infections by promoting inflammation and orchestrating opsonization of pathological material, other critical roles including disposal of immune complexes and apoptotic cellular debris [3]. In addition, it serves as a functional bridge between the innate and adaptive immune systems by enhancing antibody responses and regulating B and T cells activation, playing important roles in the development of numerous inflammatory diseases [3–5]. There are three complement pathways: classical, alternative and mannan-binding lectin (MBL) pathways .Cleavage of C3 and C5 leads to the production of the membrane attack complex [5].

Excessive and uncontrolled activation of the complement has been implicated in a series of autoimmune diseases with different pathway and mechanism such as systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), anti-neutrophil cytoplasmic antibody associated vasculitis (AAV), etc. In SLE, the predominant role of the classical pathway in initiation of complement activation, while alternative pathway amplification loop caused complement-mediated damage [4, 6, 7]. In AAV, the alternative pathway and C5a in particular acted as a bridge that links the inflammation and coagulation process [8]. As so far, the role of complement in the pathogenesis of IgG4-RD and which was the activation pathway had not been clarified.

In this study, we focus on clinical features, serum markers, treatment response and outcome in IgG4-RD with hypocomplementemia, meanwhile trying to investigate whether complement C3 and C4 levels at disease onset could be a biological marker for disease activity and prognosis.

Methods

Patients enrollment

In our prospective cohort of IgG4-RD carried out in the Peking Union Medical College Hospital (registered as ClinicalTrials.gov ID: NCT01670695), 312 newly diagnosed patients were enrolled from January 2014 to January 2019, who fulfilled the 2011 comprehensive diagnostic criteria[9,10], had complement tested at baseline and had been followed up for more than 6 months. The diagnosis of IgG4-RD was based on the following criteria: (1) a clinical examination showing characteristic diffuse/localized swelling or masses in single or multiple organs; (2) an elevated serum IgG4 concentration (>135 mg/dL); and (3) a histopathologic examination showing (a) marked lymphocytic and plasma cell infiltration and fibrosis or

(b) infiltration of IgG4+ plasma cells (a ratio of IgG4+/IgG+ cells >40% and >10 IgG4+ plasma cells per high power field). Patients with other autoimmune diseases, active infection, or malignant disease diagnosed within five year were excluded.

The study was conducted in compliance with the Declaration of Helsinki and was approved by the Ethics Committee of Peking Union Medical College Hospital (No. S-442). All patients signed written informed consent.

Clinical data and laboratory parameters

Patients' data including age, gender, disease duration, history of allergy, treatment strategy, symptom onset, organs affected, and follow-up time were collected. Allergy history was collected using the criteria from the European Academy of Allergy and Clinical Immunology. IgG4-RD responder index(RI)(2018 version) at baseline and each follow-up was evaluated[11] Laboratory parameters included routine blood analysis, liver and kidney function, erythrocyte sedimentation rate (ESR), hypersensitive C-reactive protein (hsCRP); serum complement C3 and C4，serum IgG, A, and M, IgG subclass, total IgE; rheumatoid factor and auto-antibodies tests. Affected organs and evaluation of treatment efficacy were determined by clinical symptoms, physical examinations, histopathological findings and imaging, including ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography/computed tomography (PET/CT).

Assessment of treatment outcomes

Disease response was defined as the decline of the IgG4-RD RI ≥2 points compared with baseline [12]. Clinical relapse was defined as a recurrence of symptoms and signs and/or worsening of imaging studies, with or without re-elevation of the serum IgG4 level [13]. The time of relapse was defined as the date of new onset or recurrence / exacerbation of disease based on symptoms, physical examination, laboratory or radiology findings after improvement [14].

Statistical analysis

Statistical analyses were performed using the IBM SPSS Statistics version 24.0 software (IBM, Armonk, NY, USA), the Prism software version 6.1 (GraphPad Software, La Jolla, CA, USA). Data were reported as means ± standard deviation or median and interquartile range (IQR). Normally distributed data between two groups were analyzed using independent-samples t-tests. Non-normally distributed data were analyzed with Mann–Whitney U test. Categorical data were analyzed using the chi-square test. The correlation between serum complement level and laboratory parameters was analyzed with Pearson correlation coefficient in hypocomplementemia group at baseline. Kaplan-Meier survival curves and log-rank tests were used to compare relapse-free survival. Univariate and multivariate Cox regression analysis was performed to estimate the hazard ratio (HR) of relapse for each potential risk factor. *P*-values < 0.05 were considered to represent significant differences between two groups.

Results

Demographic characteristics of IgG4-RD with hypocomplementemia

In this study, we prospectively enrolled 312 newly diagnosed IgG4-RD patients, 65(20.83%) patients had hypocomplementemia (hypocomplementemia group), 244(78.2%) patients had normal complement (normal complement group) and 3(1.0%) patients had elevated complement. Of the hypocomplementemia group, 45(69.2%) cases had both complement C3 and C4 reduction, 14(21.5%) cases with only C3 reduction, 6(9.2%) cases with only C4 reduction. As the number of cases with elevated complement was very small, we mainly compared and discussed hypocomplementemia group and normal complement group. Demographic features of such two groups were shown in Table 1. The age at diagnose in hypocomplementemia patients was 55.85±10.89 years, higher than normal complement group. The median duration of disease prior to initial evaluation was 12（4, 36） months. There was no significant difference of incidence of allergic history between two groups. Compared with normal complement group, patients with hypocomplementemia showed significantly male predominance (72.3% vs 58.6%, *P*=0.044), more number of involved organs (4.88±1.79 vs 2.89±1.36, *P*<0.001) and higher IgG4-RD RI (15.74±5.78 vs 9.64±4.33, *P*<0.001) at baseline.

Comparison of involved organs in hypocomplementemia group and normal complement group

Our data demonstrate the discrepancies in the clinical spectrums between two groups. Compared with normal complement group，patients with hypocomplementemia had significantly higher incidence of lymph node (66.2% vs 36.1%, *P*<0.001), lacrimal gland (66.2% vs 45.5%, *P*=0.003), submandibular gland (63.1% vs 41.4%, *P*=0.001), pancreas (50.8% vs 27.1%, *P*<0.001), lung (50.8% vs 18.0%, *P*<0.001), paranasal sinus (41.5% vs 27.9% *P*=0.029*)*, parotid gland (33.8% vs 11.5%,, *P*<0.001), bile duct (30.8% vs 14.3%, *P*=0.002) and prostate gland (15.4% vs 4.1%, *P* =0.021) (Table 1). There was no significant difference in kidney involvement between the two groups.

Comparison of laboratory parameters in IgG4-RD hypocomplementemia group and normal complement group

The average level of serum C3 in hypocomplementemia was 0.54±0.17g/L (normal 0.73-1.46 g/L) and C4 was 0.061±0.047 g/L(normal 0.10-0.40g/L)). We further compared the laboratory tests between two groups (Table1.), and found that patients with hypocomplementemia had significantly higher baseline levels of peripheral eosinophils count(median $0.42´10^9$/L vs $0.17´10^9$/L, *P*=0.006), ESR (46.34±32.40mm/h vs median 16mm/h, *P*<0.001), IgG (30.92±15.31 g/L vs 18.05±8.79 g/L, *P*<0.001), total-IgE (median 471.0 KU/L vs 222.0 KU/L, *P*<0.001), IgG1 (1295.11±539.48mg/dL vs 907.73±439.79mg/dL, *P*<0.001), IgG3 (100.56±80.81mg/dL vs 50.54±41.23mg/dL, *P*<0.001), IgG4 (2614.13±1915.39mg/dL vs median 547.50mg/dL, *P*<0.001), ratio of IgG4/IgG（0.80±0.44 vs 0.44±0.34, *P*<0.001), RF positive rate (42.6% vs 26.5%, *P*=0.034), whereas significantly lower count of platelet （215.80±59.00´10^9/L vs 240.30±75.80´10^9/L, *P*=0.017）, IgA (1.59±0.78g/L vs 2.36±1.32g/L, *P*<0.001).

Correlations between serum C3, C4 and clinical characteristics at baseline

We performed Pearson correlation coefficient analysis to investigate the association between serum complement level and age of onset, duration of disease, number of involved organs, IgG4-RD RI and laboratory parameters including C3/C4, count of eosinophil, ESR, hsCRP, IgG, IgA, IgM, IgE, IgG1, IgG2, IgG3, IgG4, in total patients at baseline. As shown in figure 1, level of serum C3 was negatively correlated with the age (r=-0.162, *P*=0.005), number of involved organs (r=-0.441, *P*<0.001), IgG4-RD RI (r=-0.201, *P*=0.005)，IgG (r=-0.362, *P*<0.001), IgG1(r=-0.216, *P*<0.001), IgG3 (r=-0.338, *P*<0.001) and IgG4 (r=-0.425, *P*<0.001), whereas positively correlated with serum C4(r=0.726, *P*<0.001), hsCRP (r=0.203, *P*=0.002) and IgA (r=0.341, *P*<0.001). Similarly, serum C4 level was negatively correlated with number of involved organs (r=-0.309, *P*<0.001), IgG4-RD RI (r=-0.207, *P*<0.001)，laboratory parameters such as IgG (r=-0.436, *P*<0.001), IgG1(r=-0.315, *P*<0.001), IgG3 (r=-0.301, *P*<0.001), IgG4 (r=-0.422, *P*<0.001), positively correlated with serum C3(r=0.726, *P*<0.001), hsCRP (r=0.192, *P*=0.003), IgA (r=0.224, *P*<0.001).

Treatment efficacy in IgG4-RD with hypocomplementemia

All patients with hypocomplementemia were treated with glucocorticoids (GCs), GCs combined with immunosuppressant agents (GCs plus IM) or GCs combined with rituximab (RTX). The standard induction dosage of oral prednisone was 0.6~1.0 mg $kg^{-1}day^{-1}$ in the first month and tapered per 1 or 2 weeks to the maintenance dosage.18 (27.7%) patients received GC monotherapy. One (1.5%) patient received GCs plus RTX. Others were treated with GCs plus IM, including cyclophosphamide (CYC) (n=22, 33.8%), mycophenolate mofetil (MMF) (n=12, 18.5%), methotrexate (MTX) (n=5, 7.7%), iguratimod 5(n=5, 7.7%) and leflunomide (n=1, 1.5%).

The average follow-up time of IgG4-RD patients with hypocomplementemia was 34.01±18.34 months. Level of serum C3 and C4 increased to the normal range the first month after treatment (Fig2A, B). Laboratory parameters such as ESR, hsCRP, IgG (Fig2C), IgG1 (Fig2D), IgG4 (Fig2E), IgE (Fig2F) decreased significantly after treatment. Disease response occurred in 64(98.5%) patients at month 3 and were observed quickly. One patient had no improvement at the 3rd month until increased the dosage of GCs and combined with IMs. Fifteen (23.1%) patients relapsed during follow-up with mean recurrence time 14.2±13.8 months，while only 25% of them had hypocomplementemia while relapsed.

Comparison of treatment and outcome in IgG4-RD hypocomplementemia group and normal complement group

We compared the first-line treatment between the two groups. The initial doses of GCs in hypocomplementemia group were higher than the normal complement group (37.77±14.28 vs 31.71±18.1, *P* = 0.013) (Fig3A). GC-based therapies (GC alone or in combination with IM/RTX) were used more frequently in hypocomplementemia group (100% vs 85.7%, *P*=0.001). Higher IgG4-RI and more organs involved in hypocomplementemia group, indicating that the different treatment regimens between the two groups.

To study the impact of hypocomplementemia on treatment outcomes, 45 patients with hypocomplementemia and 129 patients with normal complement followed-up more than 24 months were compared. The results showed that although IgG4-RD RI score was higher in hypocomplementemia group at baseline and 6th month follow-up（P<0.001 and P=0.005, respectively）, there was no significant difference between two groups at 12, 24, 36 and 48 months after therapy(Fig. 3C). Relapse rate was observed in 20.0%, 26.7%, 33.0%, 33.0% and 49.0% of the patients with hypocomplementemia at 12, 24, 36, 48 and 60 months after therapy, respectively. There was no significant difference of relapse rate in two groups (P=0.7559)（Fig.3D）.

Discussion

As far as we know, this is the first study to elaborate the clinical and laboratory characteristics, treatment response and prognosis of IgG4-RD with hypocomplementemia. Further,we investigated serum C3 and C4 would be biomarkers for disease activity.

In our prospective cohort, complements C3 and/or C4 were decreased in one-fifth of the IgG4-RD patients. Compared with normal complement group, IgG4-RD with hypocomplementemia was a distinct clinical phenotype, which with higher number of involved organs, higher disease activity,disparities of involved organs. John Stone suggested that IgG4-RD consisted of two overlapping subsets: a proliferative type and fibrotic type. Patients with the proliferative subset of IgG4-RD tend to have disease affecting the glandular and epithelial tissues and have high serum concentrations of IgG4, IgG1, and IgE; a higher likelihood of hypocomplementemia [15]. Our study demonstrated that IgG4-RD with hypocomplementemia had higher incidence of lymphadenopathy, dacryoadenitis, sialadenitis, autoimmune pancreatitis, lung disease, paranasal sinusitis, sclerosing cholangitis and prostate gland involvement, compared with normal complement group. Parameters associated with inflammatory and high disease activity include count of eosinophil、ESR、IgG、IgE、IgG1、IgG3 and IgG4 were significantly higher. Therefore, we think that hypocomplementemia is one of the most important features of proliferative subset.

As we known, hypocomplementemia is one important inclusion criteria associated with kidney involvement in 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-RD [16]. Kawano M reported more than 50% of patients with active IgG4-tubulointerstitial nephritis (TIN) which is the most common manifestation of IgG4-RD with kidney involvement, had hypocomplementemia [17]. However, in our cohort, there was no significant difference in renal involvement between hypocomplementemia and normal complement groups. Since apart from IgG4-TIN,IgG4-related glomerular nephritis、renal parenchymal nodule lesions and renal pelvis involvement were considered as renal involvement in our study. As Teng et al. studied 65 IgG4-related urinary disease (RUD) patients、TIN only accounted for 21(32.3%)of IgG4-RUD and mean serum C3 level of TIN group was significantly lower than other groups. Mean serum C3 and C4 were normal in group of renal pelvis or ureter involvement, abnormal renal radiological findings and renal parenchymal lesions accompanied by retroperitoneal fibrosis[18].

After one-month treatment, the average level of serum C3 and C4 in hypocomplementemia group recovered swiftly. Hypocomplementemia at baseline would not be the predictor for prognosis as there was no significant difference of relapse rate in two groups within 72 months after treatment. However,considering that patients with hypocomplementemia were given more aggressive treatment because of the higher disease activity, the predictive value of hypocomplementemia for prognosis of IgG4-RD in this study may be biased, further studies are needed.

Mechanism of complement activation in IgG4-RD remains not clear. It was reported that anti-galectin-3[19], anti-annexin A11[20], anti-laminin-511[21], and anti-prohibitin[22] had been detected in a minority of patients with IgG4-RD, for example, anti-galectin-3 antibodies were identified in approximately 30% of a cohort of 121 IgG4-RD patients with multiple organ involvement[19]. Therefore, antigen-antibody immune complex may play a role in activating complement pathway. Muraki et al proposed that based on the high serum circulating immune complex in autoimmune pancreatitis, the classical complement activation pathway is thought to be involved in IgG4-RD [23]. As we all known, IgG4 molecule does not bind complement effectively, and is unable to activate complement pathway, one plausible explanation is elevated IgG1 played a prominent role via the classical complement pathway [24, 25]. As we also found IgG1 elevated remarkably in hypocomplementemia group and serum C3,C4 were negatively correlated with IgG1. After treatment,IgG1 decreased along with the increase of serum C3 and C4 to normal in the first month，whereas the decline of IgG4 lagged behind. Another potential explanation is that IgG4 may activate the complement system through the MBL pathway [25, 26]. Sugimoto et al. reported that high serum levels of C1q-binding IgG4 in IgG4RD patients with hypocomplementemia. They observed marked reduction of total complement hemolytic (CH50) and complement activity in the classical complement pathway as well as the MBL pathway in normal human serum incubated with polyethylene glycol precipitates-immune complexes isolated from IgG4RD patients with hypocomplementemia [26]. Altered glycosylation of IgG1 and IgG4 antibody subclasses might also have a role in causing hypocomplementemia in patients with IgG4-RD[27]. Interestingly, IgA in hypocomplementemia group was significantly lower than normal complement group and positively correlated with serum C3 and C4 level. The role of IgA in the complement activation pathway remains a mystery.

In conclusion, IgG4-RD with hypocomplementemia was a distinct clinical phenotype,which had higher disease activity，higher number of affected organs and proliferative subtype features. The levels of serum C3 and C4 were negatively correlated with indicators of disease activity number of involved organs, IgG4-RI and laboratory parameters such as IgG and IgG4，implicated the complement activation system in disease pathogenesis and serum C3 and C4 could be biomarkers for disease activity. Low level of serum C3 and C4 could be recovered quickly after immunosuppressive therapy. IgG4-RD patients with hypocomplementemia respond well to treatment and have no significant difference of relapse rate in IgG4-RD patients with normal complement.

Declarations

Acknowledgements

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

LYP and HL designed the research, analyzed the data, and wrote the manuscript. JXZ, PPZ, JQL, ZL, DW, SZZ, YJY, WB, LW helped with the diagnosis, data collection, and follow-up. YYF helped with the data analysis. YZ, XFZ, FCZ and WZ designed the study and revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Peking Union Medical College Hospital. All enrolled patients consented to attend this cohort study and signed written.

Consent for publication

Yes, we obtained consent for publication from all the individuals of whom detailed information was included in the manuscript.

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Tables

Table 1. Comparison of demographic characteristics of IgG4-RD with and without hypocomplementemia at baseline.

Characteristics at baseline	Hypocomplementemia Group（n=65）	Normal Complement Group（n=244）	*P*-value
Demographic features			
Gender（male（n，%）	47（72.3%）	144（58.6%）	0.044*
Age of diagnosis, mean±SD	55.85±10.89	53.05±13.00	0.113
Duration of disease （medium months） IQR）	12（4，36）	12（6，48）	0.131
Allergy history (n, %）	40（61.5%）	125（51.2%）	0.139
Number of organs involved (mean±SD)	4.88±1.79	2.89±1.36	<0.001***
IgG4-RD RI, mean±SD	15.74±5.78	9.64±4.33	<0.001***
Organ involvement（n%）			
Lymph node	43（66.2%）	88（36.1%）	<0.001***
Lacrimal gland	43（66.2%）	111（45.5%）	0.003**
Submandibular gland	41（63.1%）	101（41.4%）	0.001**
Pancreas	33（50.8%）	66（27.1%）	<0.001***
Lung	33（50.8%）	44（18.0%）	<0.001***
Paranasal sinus	27（41.5%）	68（27.9%）	0.029*
Parotid gland	22（33.8%）	28（11.5%）	<0.001***
Bile duct	20（30.8%）	35（14.3%）	0.002**
Kidney	12（18.5%）	26（10.7%）	0.082
Prostate gland	10 (15.4%)	10(4.1%)	0.0218*
Retroperitoneum	8 (12.3%)	46 (18.9%)	0.229
Aorta/artery	5 (7.7%)	28(11.5%)	0.442
Pituitary	3（4.6%）	7（2.9%）	0.443
Gastrointestinal tract	0 (0.0%)	4(1.6%)	0.313
Mediastinum	3（4.6%）	6(2.5%）	0.349
Thyroid (Riedel's)	3 (4.6%)	10 (4.1%)	0.835
Serological features			
C3(normal 0.73-1.46 g/L)	0.54±0.17	0.99±0.33	<0.001***

C4(normal 0.10-0.40g/L)	0.061±0.047	0.19(0.14,0.25)	<0.001***
WBC(10^9/L)	6.67±1.84	6.54（5.58，7.75）	0.894
HGB(g/L)	132.35±18.38	134.37±22.07	0.508
PLT(10^9/L)	215.80±59.00	240.30±75.80	0.017*
EOS(10^9/L)	0.39(0.14,0.69)	0.19(0.10,0.33)	0.001**
ESR(mm/H)	46.34±32.40	16(7, 37)	<0.001***
hsCRP(mg/L) (<3mg/L)	2.51（0.82，8.64）	1.86（0.64，5.68）	0.117
IgG(normal 7.0-17.0g/L)	30.92±15.31	18.05±8.79	<0.001***
IgA(normal 0.7-4.0g/L)	1.59±0.78	2.36±1.32	<0.001***
IgM(normal 0.4-2.3g/L)	0.87±0.63	0.81（0.54，1.23）	0.132
IgE (KU/L)(<60KU/L)	471.0（246.75，880.00）	222.00（63.70，609.00）	<0.001***
IgG1(normal 490-1140mg/dL)	1295.11±539.48	907.73±439.79	<0.001***
IgG2(normal 150-640mg/dL)	666.83±542.76	612.56±256.77	0.259
IgG3(normal 20-110mg/dL)	100.56±80.81	50.54±41.23	<0.001***
IgG4(normal 80-135mg/dL)	2614.13±1915.39	547.50(274.23,1215.50)	<0.001***
IgG4/IgG	0.80±0.44	0.44±0.34	<0.001***
RF positive (n,%)	20(n=57, 42.6%)	44(n=166, 26.5%)	0.034*

IG4-RD RI: IgG4-RD responder index. WBC: white blood cell count. HGB: hemoglobin. PLT: platelet count. EOS: eosinophil count. ESR, estimated sedimentation rate. hsCRP: hypersensitive C-reactive protein. Ig: immunoglobulin. RF positive: the level of rheumatoid factor ³ 20 IU/ml. *P<0.05, **P<0.01, ***P<0.001.

Figures

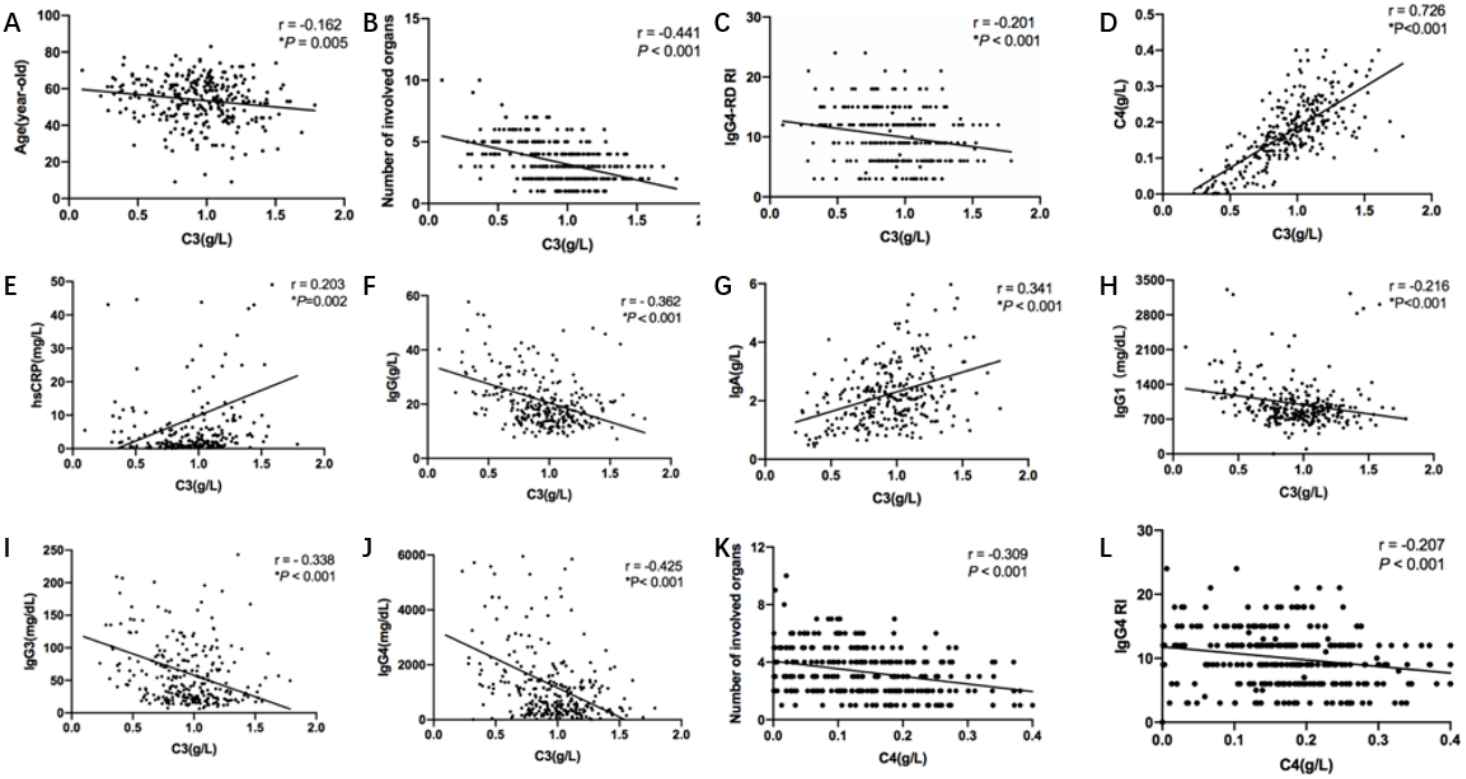

Figure 1

Correlations between baseline serum complement levels and clinical characteristics in IgG4-RD patients. (A-J) Correlations between baseline serum C3 level and clinical characteristics. (K-L) Correlations between serum C4 level and clinical characteristics.

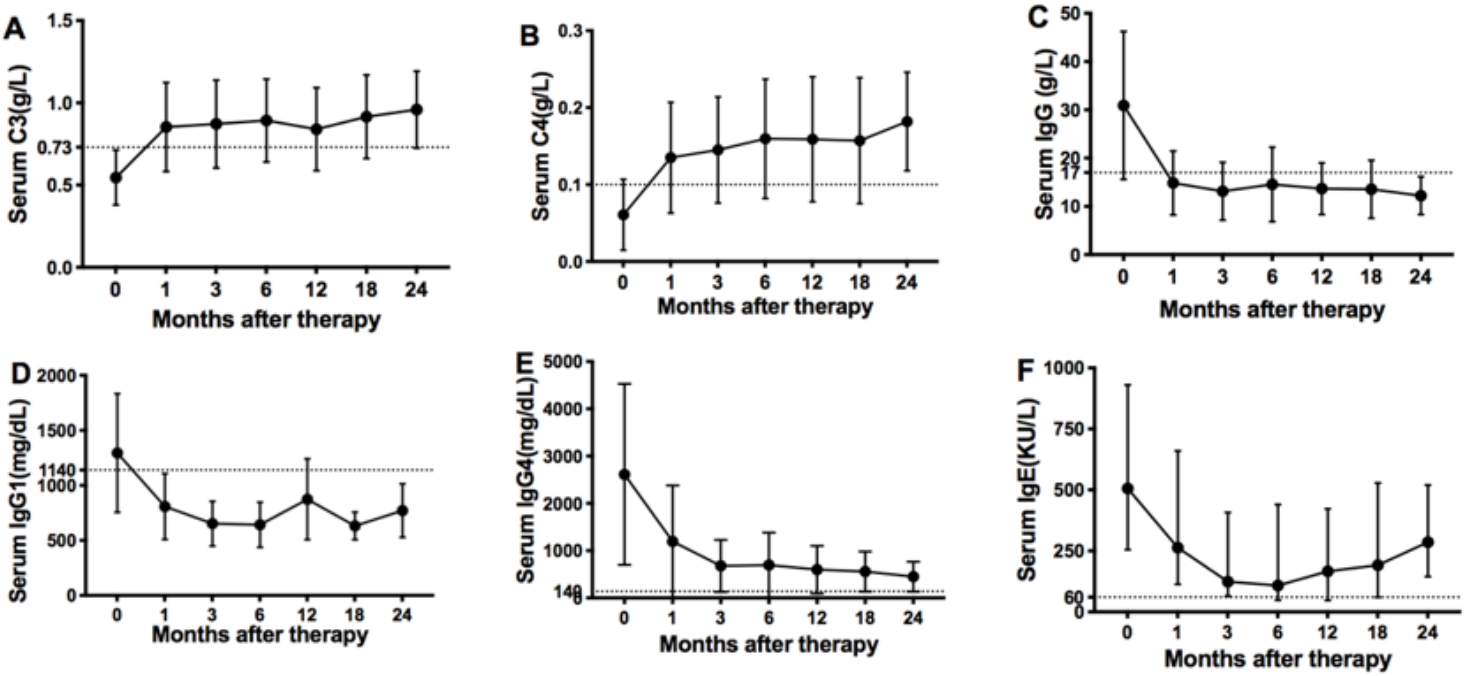

Figure 2

Changes of serum C3、C4、other laboratory parameters and IgG4-RI after treatment in IgG4-RD with hypocomplementemia. (A) Change of serum C3 after treatment in IgG4-RD with hypocomplementemia. (B) Change of serum C4 after treatment in IgG4-RD with hypocomplementemia. (C) Change of serum IgG after treatment in IgG4-RD with hypocomplementemia. (D) Change of serum IgG1 after treatment in IgG4-RD with hypocomplementemia. (E) Change of serum IgG4 after treatment in IgG4-RD with hypocomplementemia. (F) Change of serum IgE after treatment in IgG4-RD with hypocomplementemia.

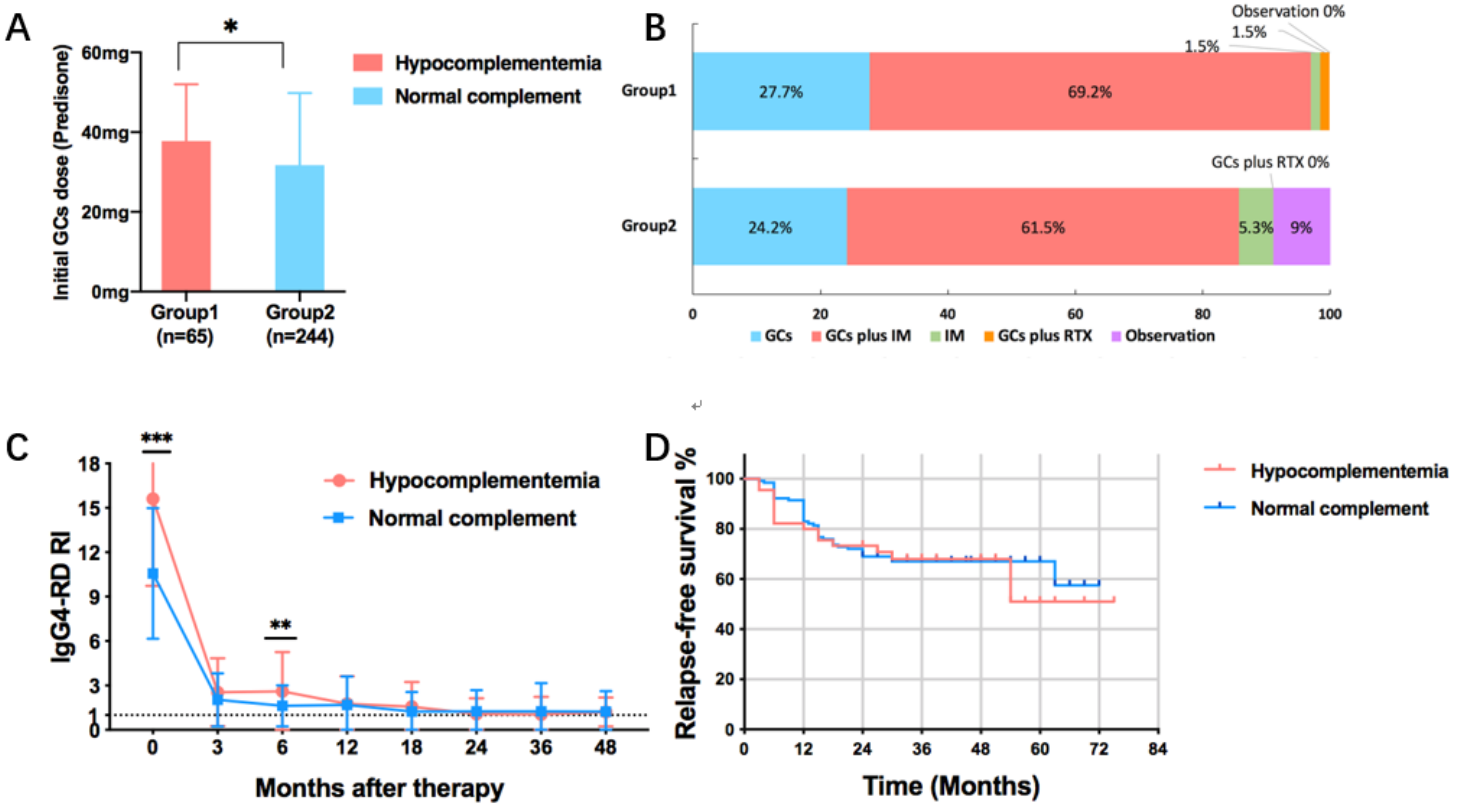

Figure 3

Comparison of treatment regimens and therapeutic outcomes of IgG4-RD patients in hypocomplementemia group and normal complement group. (A) Comparison of initial GCs dose between hypocomplementemia group (group 1) and normal group (group 2). (B) The first-line therapies for two groups. (C) The changes in IgG4-RD RI scores during the 48 months of follow-up in two groups. **P<0.01, ***P<0.001. (D) Kaplan–Meier survival curve presenting the relapse-free survival of propensity score in two groups. Relapse-free survival was defined as the period of time from the beginning of treatment to relapse (P=0.7559).