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Cardiac manifestations of eosinophilic granulomatosis with polyangiitis from a single-center cohort in China: clinical features and associated factors

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Abstract

Background: Cardiac manifestations are common and life-threatening in eosinophilic granulomatosis with polyangiitis (EGPA), which remains poorly studied in China. We aim to investigate its clinical features, associated factors, treatment, and outcomes.

Methods: We reviewed the clinical records of 110 EGPA patients and examined the independent factors associated with cardiac manifestations using multivariate logistic regression. Receiver operating characteristic curves determined the cut-off values, and survival was calculated *via* Kaplan–Meier curves.

Results: Cardiac involvement was present in 36.4% (40/110) of EGPA patients, which mainly manifested as pericardial effusion (16.4%, 18/110), myocardial involvement (13.6%, 15/110), and heart failure (8.2%, 9/110). The mean age was 42.1 ± 14.23 years with no female/male predominance. Compared with the cardiac-unaffected group, the cardiac-affected group showed a lower rate of biopsy-proved vasculitis (0% *versus* 20%, $p = 0.002$). The eosinophil count [odds ratio (OR) = 1.142, 95% confidence interval (CI) 1.029–1.267] was independently associated with cardiac manifestations in EGPA, with a cut-off value of 3.66×10^9/L [area under the curve (AUC) = 0.692, $p = 0.001$]. Regarding treatment, the cardiac-affected group displayed a higher ratio of glucocorticoid pulse combined with intravenous cyclophosphamide (CYC-IV) (40% *versus* 21.4%, $p = 0.037$), and intravenous immunoglobulin combined with glucocorticoid plus CYC-IV (17.5% *versus* 4.3%, $p = 0.035$) than the control group. Outcomes ($p = 0.131$) and survival ($p = 0.1972$) were not significantly different between the groups.

Conclusion: In this single-center Chinese EGPA cohort, cardiac manifestations are observed in 36.4% of patients, which primarily presents as myocardial involvement, pericardial effusion, and heart failure, independently associated with eosinophil count. Glucocorticoid combined with cyclophosphamide is the treatment cornerstone for EGPA patients with cardiac manifestations.

Keywords: cardiac manifestations, cardiac involvement, eosinophilic granulomatosis with polyangiitis, associated factors, treatment, outcomes

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Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly called Churg–Strauss syndrome, is the rarest type of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), predominantly affecting small to medium-sized vessels. A strong association with asthma and eosinophilia distinguishes EGPA from other forms of AAV.[1] The mean EGPA onset age is approximately 50 years with no female/male

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predominance. The annual incidence and the prevalence reported in Europe are 1.3–4.8 and 6.8–10.7 individuals per million, respectively.[2–4]

EGPA is frequently described as an evolving process.[5] The initial prodromal stage is characterized by asthma and upper respiratory symptoms.[6] The eosinophilia phase predominantly manifests as peripheral eosinophilia with organ involvement, including the lung, heart, and gastrointestinal tract. The last stage is the vasculitis phase, usually accompanied by an apparent paradoxical improvement of asthma. The organs involved in this stage are mainly the peripheral nerves, kidneys, and skin. Fewer than half of all EGPA patients are ANCA-positive, mainly presenting with myeloperoxidase ANCA.[7]

The overall mortality of EGPA is 1.53–6.9%, which is mainly caused by cardiovascular disease, respiratory system involvement, renal disease, and age higher than 65 years.[8–10] Cardiac involvement is frequent and life-threatening, contributing to about 48% of the EGPA mortality.[11] However, for the Chinese EGPA population, the relevant information remains insufficient as previous studies were primarily case reports. Hence, a systematic investigation on cardiac manifestations of EGPA in larger cohorts is required.

Therefore, we retrospectively analyzed the available clinical data of 110 EGPA inpatients at Peking Union Medical College Hospital (PUMCH) from 2007 to 2019. The study's primary aim was to summarize the characteristics of the cardiac manifestations in EGPA, and explore its independently associated factors.

Patients and methods

Patients

All patients fulfilled the criteria proposed in the 2012 Revised International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides or the American College of Rheumatology 1990 criteria, which were verified by two rheumatologists.[1,12]

For all EGPA patients, we routinely assessed heart function. Cardiac manifestations were assessed based on electrocardiogram (ECG), echocardiography, cardiac magnetic resonance, laboratory testing including myocardial enzymes, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and endomyocardial biopsy findings. The definition of cardiac manifestations was based on the previous literature but was slightly modified and made more restrictive to enable a more accurate diagnosis.[13] In particular, cardiac manifestations included pericardial effusion, myocardial involvement, heart failure, coronary lesions, valve involvement, and arrhythmia, and were defined as heart diseases that could not be explained by other reasons after consultation with experienced cardiologists. Pericardial effusion was qualitatively and quantitatively determined by echocardiography. Scanty pericardial effusion was defined as the largest dark area that was smaller than 10 mm in the pericardial cavity of the left ventricular posterior wall. Myocardial involvement included left ventricular enlargement, a left ventricular ejection fraction (LVEF) below 50% on echocardiography, and an increase in troponin I caused by noncoronary and valvular factors. Heart failure was defined as a LVEF that was less than 50% or a clinical diagnosis based on cardiac symptoms accompanied by a significant increase in NT-proBNP. A coronary lesion was defined as myocardial infarction or the degree of coronary stenosis that was more than 50% on coronary angiography, in the absence of traditional high-risk factors such as hypertension, diabetes, and hyperlipidemia. Such a lesion was considered to be caused by EGPA in consultation with cardiologists. Valve involvement was defined as moderate to severe valve insufficiency, stenosis, or thickening, except for some conditions caused by infections or genetic factors. The definition of arrhythmia was based on the ECG findings, such as a complete bundle–branch, bifascicular, or atrioventricular block; atrial fibrillation; ventricular tachycardia; and frequent ventricular premature ($\geqslant$500 beats/24 h, on a Holter monitor).

As this was a retrospective study, we only used the medical records, and oral informed consent was obtained from all enrolled patients face to face or by phone. In addition, when each patient was admitted to our hospital, our doctors stated that their clinical data may be used for scientific research, but the relevant research would not harm them and involve any private information. Therefore, all patients signed the written informed consent at that time. Furthermore, our study was approved by the Medical Ethics Committee of PUMCH (Beijing, China, approval number: S-K1385).

Clinical and laboratory assessment

To assess the disease activity better and develop appropriate treatment strategies, we examined each system for all of the patients diagnosed with EGPA. The definition of arthritis was based on the symptoms of swelling and pain in multiple joints, accompanied by morning stiffness. Severe asthma was defined as asthma that required continuous glucocorticoid (GC) therapy (a high dose of an inhaled, oral, or intravenous GC) or asthma with persistent dyspnea. Cutaneous vasculitis included palpable purpura, reticulata, or gangrene of the extremities. Renal involvement was defined as the presence of active urinary sediment (hematuria or cylindruria), proteinuria (urine protein $>0.5\,g/24\,h$), or serum creatinine beyond the upper limit of the normal range. Digestive system involvement was defined as gastrointestinal bleeding, intestinal obstruction, or digestive tract conditions that other mechanisms could not explain. Peripheral nervous system involvement included mononeuritis multiplex and multiple peripheral neuropathy (mononeuritis multiplex meant simultaneous or successive involvement of two or more separate non-adjacent nerve trunks, and multiple peripheral neuropathy predominantly affected the distal extremities in a bilaterally symmetrical distribution). The definition of central nervous system involvement combined clinical manifestations with magnetic resonance imaging (MRI) or computed tomography (CT) scan, including intracranial ischemia or hemorrhages, spinal cord or medulla oblongata involvement, hypertrophic cranial pachymeningitis, posterior reversible encephalopathy syndrome, and cerebellar ataxia. Sinusitis was diagnosed based on the patients' clinical symptoms, physical examination, and MRI findings. In this cohort, vital organ involvement was defined as the lesions of one or more organs in the respiratory system, digestive system, kidney, or peripheral nervous system.

The 2011 revised five-factor score (FFS) system[14] and the original 1994 Birmingham vasculitis activity score (BVAS)[15] were used to evaluate the prognosis and disease activity of vasculitides at diagnosis. Refractory EGPA was defined as a progressive condition unresponsive to GC and cyclophosphamide (CYC).[16] Complete remission (CR) and partial relief (PR) were defined as a BVAS of 0 and a decrease of 50% or more in the BVAS from the baseline value, respectively. Considering that only mild pericardial effusion without severe cardiac manifestations possibly had no significant effect on the outcomes and survival, we excluded these patients from the cardiac-affected group and defined it as a part of the control group for this analysis.

Statistical analysis

The statistical analysis was performed using Statistical Product and Service Solutions (International Business Machines Corporation 25, Armonk, NY, USA). The quantitative data of the normal and non-normal distributions were expressed as the mean ± standard deviation (SD) and median and interquartile range (IQR) and were compared using the unpaired *t*-test and Mann–Whitney *U* test, respectively. The categorical variables were expressed as frequencies and percentages and were compared using Fisher's exact test or chi-square analysis.

The clinical data of patients with cardiac manifestations, also described as the cardiac-affected group, were compared to those without cardiac manifestations, described as the cardiac-unaffected or control group. Factors with a two-sided p value < 0.05 were included in the multivariate logistic regression analysis. These were presented with odds ratios (ORs) and 95% confidence intervals (CIs). Receiver operating characteristic (ROC) curves were used to determine the cut-off values of the eosinophil count for cardiac manifestations in EGPA according to the area under the curve (AUC), sensitivity, and specificity (MedCalc application; MedCalc Software, Ostend, Belgium). Kaplan–Meier survival curves and log-rank tests illustrate and compare the cumulative survival rates (Prism 7; GraphPad, San Diego, CA, USA). A two-sided p value < 0.05 was considered a statistically significant difference.

Results

Characteristics of cardiac manifestations

A total of 110 hospitalized EGPA patients was enrolled in this study. Forty patients (36.4%) were found to have cardiac manifestations related to EGPA. The average EGPA onset age was 42.1 ± 14.23 years (range 19–80 years) with no female/male predominance. The clinical features of cardiac involvement in EGPA are summarized in Table 1. Pericardial effusion occurred in 18

Table 1. Characteristics of cardiac manifestations in EGPA.

Type	Number	Percentage (%)
Pericardial effusion	18	16.36
Myocardial involvement	15	13.64
Global left ventricular hypokinesis	7	46.67
Left ventricular systolic dysfunction	6	40.00
Left ventricle enlargement	2	13.33
Troponin I elevation	8	53.33
Heart failure	9	8.18
Coronary lesion	6	5.45
Myocardial infarction	5	83.33
Coronary spasm	1	16.67
Arrhythmia	4	3.64
Valve insufficiency	3	2.73

EGPA, eosinophilic granulomatosis with polyangiitis.

cases (16.4%), in most of whom (16 cases, 88.9%), the effusion was scanty. Fifteen patients (13.64%) developed myocardial involvement, including one case of acute myocarditis. Laboratory tests revealed an elevated troponin I in eight cases (53.33%) with no dynamic changes in the ECG and myocardial enzymes. Therefore, the possibility of myocardial infarction in these patients was ruled out.

Coronary involvement occurred in six cases (5.5%), including five men and one woman. Among them, five cases (four men and one woman, aged 23–48 years) were diagnosed with myocardial infarction, of which four were acute, and one was an old myocardial infarction. Especially in one patient, coronary angiography revealed proximal stenosis that exceeded 50%, which was from a 25-year-old woman without hypertension, hyperlipidemia, or other risk factors related to arteriosclerosis-associated heart disease, and the heart symptoms were secondary to EGPA. The remaining one case only presented as coronary spasm with chest pain.

Heart failure developed in nine patients (8.2%), which included six cases with LVEF below 40% (the lowest value was 31%) and three patients with obvious symptoms of heart failure, and all the patients were accompanied by significantly elevated NT-proBNP (mean 4592 pg/ml). In addition, arrhythmias were observed in four cases (3.6%), including one case with third-degree atrioventricular block, one case with left anterior bundle–branch block, one with frequent premature ventricular beats (903 beats/24 h), and another one with multiple premature ventricular beats with couplets and ventricular tachycardia. Moderate valve insufficiency developed in three patients, all of whom were affected the mitral valve.

Clinical features of EGPA patients at baseline

Compared with the cardiac-unaffected group, the cardiac-affected group had a higher proportion of patients under 30 years of age (25% *versus* 10%, $p=0.036$), and a shorter disease duration [4.0 (1.0, 11.8) *versus* 6.0 (2.8, 24.0) months, $p=0.033$)]. Laboratory testing results showed that the eosinophil count was significantly higher in the cardiac-affected group than in the cardiac-unaffected group [4.52 (2.41, 9.73) *versus* 2.20 (0.92, 5.38) $\times 10^9$/L, $p=0.002$]. The proportion of FFS $\geqslant 2$ in the cardiac-affected group was higher than that in the cardiac-unaffected group (55.0% *versus* 12.9%, $p<0.0001$). Furthermore, the cardiac-affected group revealed a significantly lower percentage of

biopsy-proven vasculitis than the cardiac-unaffected group (0% *versus* 20%, $p=0.002$). All other findings concerning the clinical manifestations and laboratory tests are shown in Table 2.

Furthermore, we analyzed the relationship between cardiac manifestations and the number of vital organs involved. We found that the patients with severe cardiac manifestations had a higher proportion of one or more vital organs involved than that in the control group (100% *versus* 87%, $p=0.031$; Supplemental Table 1), although no significant differences were observed in any specific vital organ involved between the groups (Table 2). We also summarized and compared the main clinical features of EGPA from several large cohort studies (Supplemental Table 2).

Independently associated factors for cardiac manifestations in EGPA patients

Factors significantly associated with cardiac manifestations or with important clinical significance were selected by further multivariate analysis. We found that the eosinophil count (OR = 1.142, 95% CI 1.029–1.267) was the only independent factor significantly associated with cardiac involvement in EGPA (Table 3).

ROC analysis for identifying cardiac involvement in EGPA

ROC curve analysis was used to determine the cut-off value of the eosinophil count. The results showed that the optimal cut-off value was 3.66×10^9/L (AUC = 0.692, $p=0.001$, sensitivity 72.73%, specificity 67.80%; Figure 1).

Treatment and outcomes

All patients from the cardiac-affected group were administered with GC, including 16 cases (40.0%) of GC pulse (0.5~1.0 g/day, 3~5 days), 21 cases (52.5%) of high-dose GC (1~2 mg/kg/day), and three cases of medium-dose GC (0.5~0.8 mg/kg/day). Furthermore, 97.5% of the EGPA patients were administered with GC combined with CYC. Compared with the treatment administered to the control group, the cardiac-affected group had a significantly higher proportion of patients who received GC pulse combined with intravenous cyclophosphamide (CYC-IV) (40% *versus* 21.4%, $p=0.037$), and intravenous immunoglobulin (IVIG) combined with GC plus CYC-IV (17.5% *versus* 4.3%, $p=0.035$) (Table 4). In addition, a small number of patients were also prescribed other traditional immunosuppressants including methotrexate (six cases), azathioprine (six cases), *Tripterygium wilfordii* (used in traditional Chinese medicine; two cases), tacrolimus (two cases), leflunomide (two cases), and cyclosporine A (one case). Special therapies, including rituximab and plasma exchange (one case for both), were used for some refractory EGPA patients.

Concerning the outcomes of patients with severe cardiac manifestations, 84.8% of the 110 patients achieved CR, and 3.0% experienced PR after active follow-up and treatment. The overall outcomes were not significantly different ($p=0.131$; Table 4). In the forty cardiac-affected EGPA patients, we further retrospectively analyzed the differences in the outcomes between the patients who had ever used IVIG at least once and those who had never used IVIG (Supplemental Table 3). We found that all deaths occurred in the group who had never received IVIG therapy, although it did not show a statistically significant difference between the groups.

Besides, Kaplan–Meier survival analysis showed that the 5-year cumulative survival rates in patients with and without severe cardiac involvement were 86.8% and 94.4%, respectively. No statistical difference was found between the two groups (log-rank test $p=0.1972$; Figure 2).

Discussion

This study's key findings were as follows. Cardiac manifestations occurred in 36.4% of all EGPA patients in the single-center Chinese EGPA population, which primarily presented as pericardial effusion, diffuse myocardial involvement, and heart failure. A raised eosinophil count was found to be the only independent factor associated with cardiac manifestations in EGPA. The overall treatment intensity for patients with cardiac involvement was higher than that for patients without cardiac involvement. GC combined with CYC was still the treatment cornerstone for EGPA patients with cardiac involvement.

Cardiac manifestations are significant and sometimes very severe complications of EGPA. In our cohort, approximately one-third of the EGPA patients developed cardiac damage. The proportion of cardiac involvement in EGPA varies

Table 2. Baseline features of EGPA patients with or without cardiac manifestations.

Characteristics	With cardiac manifestations, *n* = 40	Without cardiac manifestations, *n* = 70	*p* value
Demographics			
Age (years, x ± S)	42.1 ± 14.23	46.7 ± 13.24	0.095
<30 years, *n* (%)	10 (25)	7 (10)	0.036*
Gender (male/female, number)	21/19	39/31	0.745
Time from allergy to EGPA diagnosis (month), median (IQR)	31.0 (5.0, 63.5)	24.0 (4.8, 82.5)	0.667
Disease duration (month), median (IQR)	4.0 (1.0, 11.8)	6.0 (2.8, 24.0)	0.033*
Time from initial symptoms to EGPA diagnosis (month), median (IQR)	24.0 (0.3, 48.0)	5.0 (0, 37.5)	0.143
Clinical manifestation [*n* (%)]			
Weight loss	13 (32.5)	28 (40.0)	0.434
Fever	16 (40.0)	29 (41.4)	0.883
Arthritis	5 (12.5)	12 (17.1)	0.517
Myalgia	7 (17.5)	15 (21.4)	0.620
Allergic rhinitis	15 (37.5)	25 (35.7)	0.851
Severe asthma	33 (82.5)	52 (74.3)	0.323
Cutaneous vasculitis	19 (47.5)	40 (57.1)	0.329
Renal involvement	8 (20.0)	20 (28.6)	0.321
Digestive tract involvement	14 (35.0)	22 (31.4)	0.701
Peripheral neuropathy	20 (50.0)	31 (44.3)	0.563
CNS involvement	5 (12.5)	14 (20.0)	0.317
Ear involvement	4 (10.0)	10 (14.3)	0.516
Sinusitis	25 (62.5)	39 (55.7)	0.488
Laboratory examination			
Eos count (10^9/L), median (IQR)	4.52 (2.41, 9.73)	2.20 (0.92, 5.38)	0.002*
ESR [mm/1h, median (IQR)]	34 (11, 59)	30 (12, 50)	0.683
CRP [mg/L, median (IQR)]	26.0 (4.9, 79.7)	19.9 (4.2, 49.4)	0.428
RF [IU/mL, median (IQR)]	28 (10, 67)	24 (8, 138)	0.441
MPO ANCA, *n* (%)	4 (10.0)	11 (15.7)	0.401
BVAS,‡ median (IQR)	17.0 (12.5, 22.5)	13.5 (9.0, 19.0)	0.251
FFS ⩾ 2, *n* (%)	22 (55.0)	9 (12.9)	<0.0001*
Biopsy-proven vasculitis	0 (0)	14 (20)	0.002*

(Continued)

Table 2. (Continued)

Characteristics	With cardiac manifestations, *n* = 40	Without cardiac manifestations, *n* = 70	*p* value
Thrombotic event, *n* (%)	2 (5.0)	5 (7.1)	1.000
Granuloma, *n* (%)	1 (2.5)	5 (7.1)	0.414

‡Considering that the cardiac manifestations itself are included in BVAS, which made the comparison between the cardiac-affected group and the control group biased, we did not include the score of the cardiac manifestations when calculating the BVAS.
*$p < 0.05$ was considered a significant difference between the two groups.
ANCA, anti-neutrophil cytoplasmic antibody; BVAS, Birmingham Vasculitis Activity Score; CNS, central nervous system; CRP, C-reactive protein; EGPA, eosinophilic granulomatosis with polyangiitis; Eos, eosinophil; ESR, erythrocyte sedimentation rate; FFS, five factor score; MPO, myeloperoxidase; PR3, protease 3; RF, rheumatoid factor.

Table 3. Multivariate analysis for 40 EGPA patients with cardiac manifestations and 70 controls.

Variable	OR (95% CI)	*p* value
Eos count (10^9/L)	1.142 (1.029–1.267)	0.012*
MPO-ANCA positivity	0.483 (0.124–1.885)	0.295
Disease duration (month)	0.975 (0.947–1.004)	0.088
Age (years)	0.983 (0.949–1.018)	0.331

*$p < 0.05$ was considered a significant difference between the two groups.
ANCA, antineutrophil cytoplasmic antibody; CI, confidence interval; Eos, eosinophil; EGPA, eosinophilic granulomatosis with polyangiitis; MPO, myeloperoxidase; OR, odds ratio.

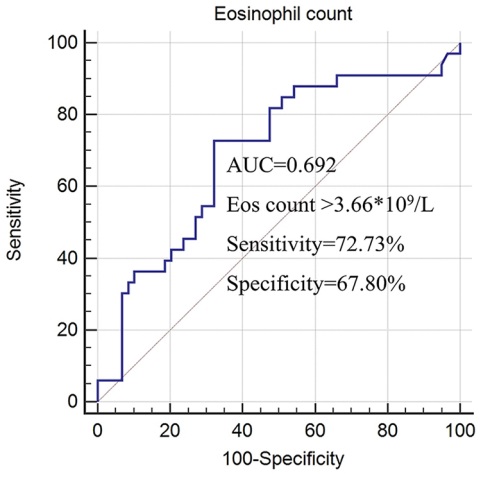

Figure 1. The receiver operating characteristic (ROC) curve of eosinophil count for identifying cardiac manifestations in eosinophilic granulomatosis with polyangiitis (EGPA).
AUC, area under the curve; Eos, eosinophil.

significantly from 11.2% to 92% according to previous reports.[17–20] There may be a variety of reasons for these differences. First, there is no uniform definition for cardiac involvement in EGPA. For example, some studies have included EGPA patients with impaired diastolic function or mild valve insufficiency in the category of cardiac manifestations.[21] These indicators may be unspecific. Moreover, the population, region, range of years, and sample size may also influence the proportion of cardiac involvement.

The mechanism through which AAVs target the heart focuses on small-vessel vasculitis, but the ratio of cardiac involvement in different forms of AAV varies. According to reported data, cardiac involvement was clinically observed in 3.3–13.0% and 20–24% of patients with granulomatosis with polyangiitis and microscopic polyangiitis, respectively.[14,22,23] These percentages are lower than those in EGPA. The reason may be that in EGPA, eosinophilic infiltration into the cardiac pericardium or myocardium plays a vital role in the pathogenesis of cardiac involvement.[24]

Our cohort revealed that cardiac manifestations in EGPA commonly present as pericardial effusion, myocardial involvement, heart failure, and

Table 4. Treatment and outcomes of EGPA patients with and without cardiac manifestations.

	With cardiac manifestations	Without cardiac manifestations	*p* value
Treatment, *n* (%)	40 (36.4)	70 (63.6)	
GC	40 (100)	67 (95.7)£	0.552
CYC	39 (97.5)	59 (84.3)	0.053
GC pulse+CYC-IV	16 (40.0)	15 (21.4)	0.037*
IVIG	8 (20)	6 (8.6)	0.084
IVIG+CYC-IV	7 (17.5)	3 (4.3)	0.035*
Rituximab	1 (2.5)	0 (0)	0.364
Plasma exchange	1 (2.5)	0 (0)	0.364
Outcomes,‡ *n* (%)	33 (30)	77 (70)	0.131
Complete remission	28 (84.8)	62 (80.5)	0.590
Partial relief	1 (3.0)	11 (14.3)	0.103
Death	4 (12.1)	4 (5.2)	0.238

All patients with cardiac manifestations used GC, and we just compared the main remission-inducing drugs. Therefore, the above treatments were all based on GC therapy and other immunosuppressive drugs may also be used in different treatment stages.
£Three patients in the cardiac-unaffected group did not use GC, two of which were due to hepatitis B virus replication and airway tuberculosis, respectively, and the other patient did not follow doctor's advice.
‡Here we excluded those patients only with mild pericardial effusion from the cardiac-affected group and included them in the control group, and perform chi-square test or Fisher's exact test.
*$p < 0.05$ was considered a significant difference between the two groups.
CYC-IV, intravenous infusion of cyclophosphamide; EGPA, eosinophilic granulomatosis with polyangiitis; GC, glucocorticoid (including pulse, high-dose and medium-dose); GC+CYC, glucocorticoid plus cyclophosphamide (including all kinds of dosages); IVIG, intravenous immunoglobulin.

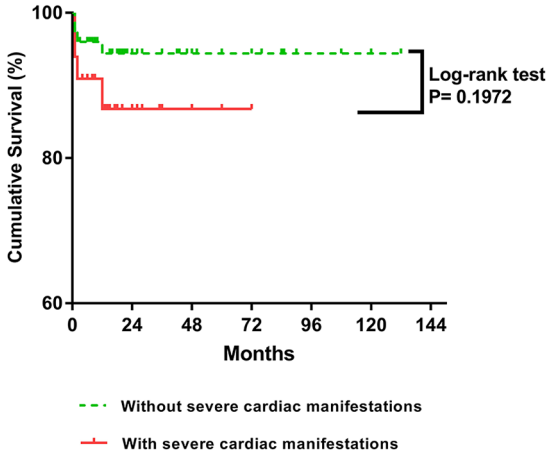

Figure 2. Comparison of cumulative survival rates between eosinophilic granulomatosis with polyangiitis (EGPA) patients with and without severe cardiac manifestations.

coronary involvement, consistent with the findings in other studies.[11,25] According to the existing research on EGPA, activated eosinophils may cause direct myocardial damage by secreting granule proteins, including major basic protein, neurotoxins, and cationic protein.[26,27] Many cytokines, such as interleukin (IL)-5, IL-4, IL-13, are released by the overactivated eosinophils and lymphocytes.[28] All these factors participate in the general inflammatory process and may lead to both non-specific symptoms and pericarditis.

The eosinophil count was found to be the only independent factor associated with cardiac manifestations in EGPA. We performed further analysis to determine its cut-off value for cardiac involvement, which, with good sensitivity, was 3.66×10^9/L. Several studies reported that the absolute eosinophil count before treatment was

higher in rhythm disturbances and inversely correlated with left ventricular systolic function.[21,29] Notably, we observed that compared with the cardiac-unaffected group, the cardiac-affected group showed a higher ratio of patients under 30 years of age. Moreover, those EGPA patients who developed severe coronary involvement and died early were often relatively young. One study indicated that younger EGPA patients were more likely to develop cardiomyopathy, and their prognosis was poorer.[30]

In other investigations, ANCA negativity was frequent in EGPA patients with cardiac involvement,[31,32] although no significant difference was found in our study. We speculate that it is because ANCA positivity was relatively uncommon in our cohort, and the sample size was not large enough. However, we found that the proportion of biopsy-proven vasculitis in the cardiac-affected group was significantly lower than that of the cardiac-unaffected group, which implies that EGPA-complicated cardiac manifestations may primarily be mediated by eosinophils rather than vasculitis.

Regarding treatment and outcomes, almost all patients with cardiac manifestations were treated with high-dose GC and CYC as the initial therapy. Among these patients, nearly half of them received GC pulse combined with CYC-IV. In this study, we also tried IVIG therapy for eight EGPA patients with cardiac involvement who did not respond well to the standard treatment (GC plus immunosuppressant). All of these patients ultimately achieved complete or partial remission. Other studies also recommended IVIG as an adjunctive therapy.[33–35] IVIG preparations have been revealed by which anti-idiotype antibodies might play a role in neutralizing pathogenic ANCAs. However, in EGPA, which has a high proportion of ANCA negativity, IVIG therapy also showed similar efficacy to that shown in other AAVs,[34] which implied that there may exist other mechanisms. Studies have speculated that IVIG could exert cytotoxic effects on eosinophils, mediated by natural anti-Siglec-8 autoantibodies in IVIG preparations.[36] However, in clinical practice, because IVIG is still too expensive for most patients to access in China, we generally use it for few refractory EGPA patients.

Overall, in the cardiac-affected group, the clinical remission rate was 87.8%, indicating the treatment strategy's effectiveness. Finally, there were no statistical differences in the outcomes and survival rates between the two groups, which seems inconsistent with previous studies that reported that cardiac involvement may decrease survival rates.[37,38] The main reason for this may be that our follow-up duration was relatively short. From the results of another cohort study in Germany, we observed that the survival rate hardly changed within 5 years, and only after 72 months did the survival rates gradually show differences. The most significant difference occurred after 10 years,[37] because EGPA-related cardiac involvement is a slowly progressing process, especially for heart failure. The related deaths may occur 5 or even 10 years later. It prompts us to consider that close follow-up is needed between 5 and 10 years as this period may significantly impact the patients' prognosis. Therefore, we will continue to observe long-term outcomes. The other possible reasons include that our sample size was inadequate, and the treatment was more aggressive in the cardiac-affected group, especially in the use of high-dose IVIG.

Furthermore, towards the end of the follow-up period, the long-term mortality in the cardiac-affected group did not increase significantly compared with the control group, suggesting that the outcomes of patients with cardiac manifestations were generally good after timely diagnosis and effective treatment. Studies have revealed that cardiac involvement was a strong mortality predictor in EGPA,[39,40] however, in our cohort, most patients responded well to GC combined with immunosuppressants, and their heart function recovered well. Insights into EGPA pathogenesis have highlighted newer therapies such as mepolizumab targeting IL-5; however, this has only been supported in non-severe manifestations of EGPA.[41–43] For severe complications, GC, traditional immunosuppressants, and IVIG are still the most effective treatment.[44]

There were inevitable limitations to this study. First, as this was a retrospective study, we could not make a causal inference for the risk factors of cardiac involvement and the IVIG's effectiveness. Second, all of the cases were inpatients from a large tertiary hospital, and most of them were referral patients who had been treated in local

hospitals, whose conditions were generally worse. Thus, this EGPA cohort may not be extrapolated to the entire Chinese population. Furthermore, we recognize the need to include more EGPA patients to clarify ANCA's characteristics in cardiac manifestations of EGPA, as well as the need for continued follow-up to observe the impact of cardiac manifestations on the EGPA patients' long-term survival. We hope to conduct a prospective multicenter cohort study in China to obtain more comprehensive conclusions in the future.

Conclusion

Cardiac manifestations are frequent in EGPA and mainly present with diffuse myocardial involvement, pericardial effusion, and heart failure. The manifestations may affect the coronary arteries, causing myocardial infarctions. A raised eosinophil count is the factor independently associated with cardiac involvement, and its value over 3.66×10^9/L helps identify cardiac involvement. Active treatment, primarily by GC plus CYC, may improve patients' outcomes and overall survival rate.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

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