Rheumatoid factor positivity in granulomatosis with polyangiitis: implications for clinical outcomes and immunological profiles

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Abstract

Objective

Granulomatosis with polyangiitis (GPA) is a systemic necrotising vasculitis marked by granulomatous inflammation and small-vessel involvement. Rheumatoid factor (Rf) positivity is classically linked to rheumatoid arthritis but is also observed in other autoimmune diseases, including GPA. However, the clinical implications of Rf positivity in GPA remain uncertain. The research aims to evaluate the impact of Rf positivity on clinical and laboratory parameters, organ involvement patterns, disease activity, and outcomes in GPA patients.

Methods

The single-centre cohort of 82 GPA patients were analysed retrospectively, with the patients categorised as Rf + (n=37) and Rf - (n=45). Data were collected on demographic features, laboratory findings, clinical manifestations, treatment, and outcomes. Appropriate statistical methods were employed to evaluate differences between groups.

Results

Rf+GPA patients exhibited significantly higher levels of c-ANCA, total protein-to-albumin ratio, white blood cells (WBCs) count, neutrophil-to-lymphocyte ratio, and Birmingham Vasculitis Activity Score (BVAS), indicating heightened inflammatory and immunological activity. Arthritis was significantly more prevalent in Rf + patients, whereas skin involvement was inversely associated with Rf positivity. Despite similar overall disease durations, end-stage renal disease (ESRD) prevalence was lower in Rf + patients, potentially related to higher rituximab usage in this group.

Conclusion

Rf positivity in GPA is associated with distinct clinical and immunological profiles, including an arthritis-dominant phenotype and reduced skin involvement. These findings suggest that Rf may influence disease course and organ involvement patterns, highlighting its potential as a biomarker for identifying distinct clinical phenotypes in GPA management.

Key words

granulomatosis with polyangiitis, rheumatoid factor, arthritis, disease activity, rituximab.

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Introduction

Granulomatous polyangiitis (GPA) is a rare and complex autoimmune disease characterised by necrotising granulomatous inflammation. Clinically, GPA can present in various forms, ranging from limited disease, which may only involve the upper respiratory tract, to more severe systemic involvement with renal failure and pulmonary complications (1, 2). The aetiology of GPA remains largely unknown, although it is associated with the presence of anti-neutrophil cytoplasmic antibodies (ANCA), specifically those targeting proteinase 3 (PR3) (3, 4).

Rheumatoid factor (Rf) is an autoantibody primarily associated with rheumatoid arthritis (RA). Rf is directed against the Fc region of immunoglobulin G (IgG) antibodies and is found in the serum of many patients with autoimmune disease. The presence of Rf is not exclusive to RA; it can also be detected in other autoimmune diseases and infections (5, 6).

Rf positivity has been associated with a more severe clinical course in autoimmune diseases, particularly RA, encompassing increased disease activity, reduced functional capacity, and a higher frequency of extra-articular manifestations. In contrast, Rf- conditions, such as Sjögren's syndrome (SjS) and systemic lupus erythematosus (SLE), frequently exhibit distinct autoantibody profiles and may present with less prominent joint involvement (7, 8). Recent studies have suggested that heterogeneity in autoantibody expression and immune response pathways may contribute to the clinical variability observed in ANCA-associated vasculitis (AAV), including GPA (9). Considering the established role of Rf in modulating inflammatory and autoimmune processes, this study aimed to assess the influence of Rf positivity on laboratory parameters, clinical features, organ involvement distributions, treatment responses, and clinical outcomes in patients with GPA. We hypothesised that Rf positivity could define a distinct clinical and immunological phenotype within the GPA spectrum, and sought to investigate whether Rf+ GPA patients exhibit specific inflammatory profiles, organ involvement characteristics, and clinical outcomes compared to Rf- individuals.

Materials and methods

This retrospective, single-centre cohort study included patients diagnosed with GPA between 2014 and 2024 at a university-based rheumatology clinic. Ethical approval was obtained from the local institutional ethics committee. Inclusion criteria were: age ≥18 years at the time of diagnosis; fulfillment of the 2022 ACR/EULAR classification criteria for GPA; and availability of comprehensive clinical, laboratory, and treatment data at baseline and during follow-up. Patients were excluded if they (1) had comorbid systemic autoimmune diseases such as RA, SLE or SjS; (2) presented with active infection or malignancy at the time of diagnosis; or (3) had incomplete or missing key data. The final study population comprised 82 adult patients, categorised into two groups based on Rf status: 37 Rf+ and 45 Rf- individuals. Patients were categorised as Rf+ if their Rf levels exceeded the laboratory's established reference threshold for positivity. Given the retrospective design and the rarity of GPA, a formal sample size calculation was not performed. Instead, all eligible patients diagnosed between 2014 and 2024 who met the inclusion criteria were included in the study. All clinical, laboratory, and treatment-related data were obtained from electronic medical records and hospitalisation reports, supplemented by manual verification to ensure accuracy and completeness. The data collection process included sociodemographic variables, laboratory test results at diagnosis, and clinical characteristics. Clinical involvement details, Birmingham Vasculitis Activity Score (BVAS), mortality rates, and infection-related hospitalisations were systematically recorded to ensure a comprehensive assessment of patient outcomes.

Statistical analyses were performed using Jamovi (v. 2.6.22). The Levene's test assessed variance homogeneity, and the Shapiro-Wilk test evaluated normality. Non-normally distributed data were analysed with the Mann-

Whitney U-test, while normally distributed data were analysed using the independent samples t-test. Categorical variables were assessed using the Chi-square test or Fisher's exact test, as appropriate. In GPA patients, logistic regression analysis using the Backward Stepwise, Wald method was conducted to predict the development of end-stage renal disease (ESRD). The results were presented with the constant term, odds ratio (OR), *p*-values, and 95% confidence intervals (CI). A *p*-value of <0.05 was considered statistically significant.

Results

In this retrospective single-centre cohort study conducted over a 15-year period (2010–2024), a total of 82 patients were diagnosed with GPA within a population of approximately 750,000 individuals. A total of 37 patients were identified as Rf+, while 45 were identified as Rf-. The Rf positivity rate among these GPA patients was 45.1%, corresponding to a cumulative prevalence of 4.9 per 100,000 individuals. Among the Rf+ patients, 13 individuals (35%) exhibited low-positive Rf levels, as defined by the 2010 ACR/EULAR classification criteria for RA (10). Anti-CCP antibody testing was available for all 37 Rf+ patients, and only one patient (2.7%) tested positive for anti-CCP antibodies.

The analysis of clinical and laboratory parameters between patients with Rf+ and Rf- GPA is presented in Table I.

The mean age of Rf+ patients was 46.8±12.6 years, compared to 52.4±14.9 years in Rf- patients (*p*=0.083). The overall disease duration was similar, with Rf+ patients averaging 230.2±213.2 weeks and Rf- patients 200.2±171.7 weeks (*p*=0.658). Additionally, the time to mortality post-disease onset was similar, with Rf+ patients at 121.6±159.4 weeks and Rf- patients at 50.6±51.8 weeks (*p*=0.457).

Significant differences were observed in several laboratory parameters: c-ANCA (Elisa) (AU/mL) levels were higher in Rf+ patients (80.3±28.5) compared to Rf- patients (52.2±42.9) (*p*=0.006). Urea levels (mg/dL) were lower in the Rf+ group (58.8±56.3) compared to the Rf- group (89.5±77.6) (*p*=0.029). Additionally, the uric acid to creatinine ratio was higher in Rf+ patients (5.07±2.69) than in Rf- patients (3.76±2.35) (*p*=0.030).

Haematological parameters revealed a significantly higher white blood cells (WBCs) count (10e3/μL) in Rf+ patients (12.3±4.25) compared to Rf- patients (10.6±4.58) (*p*=0.046), and an elevated neutrophil to lymphocyte ratio (NLR) in Rf + patients (11.71±8.69) *versus* Rf- patients (8.08±8.03) (*p*=0.016). Disease activity parameters revealed a significantly higher BVAS in Rf+ GPA patients (19.5±7.10, min-max: 7–39) compared to Rf- GPA patients (16.5±6.65, min-max: 7–31) (*p*=0.047).

Among biochemical parameters, alkaline phosphatase (ALP) levels (IU/L) were significantly lower in Rf+ patients (76.2±40.2) compared to Rf- patients (95.7±55.6) (*p*=0.038). Total protein/albumin ratio was significantly higher in Rf+ patients (1.95±0.20) compared to Rf- patients (1.86±0.31) (*p*=0.027). No statistically significant differences were observed in other haematological and biochemical parameters.

Table II presents the results of the analysis examining the relationship between Rf positivity and various demographic, clinical parameters, and treatment characteristics in GPA patients.

The analysis of gender distribution in GPA patients showed no significant difference between Rf+ and Rf- groups (*p*=0.267). Similarly, ANCA (Ifa) (PR3 a/o MPO ANCA) positivity did not dif-

Table I. Comparative analysis of clinical parameters in GPA patients according to Rf positivity status.

	Rf positives (n=37)	Rf negatives (n=45)	*p*-value
Age (years)	46.8 ± 12.6	52.4 ± 14.9	0.083 [x]
c-ANCA (Elisa) (AU/mL)	80.3 ± 28.5	52.2 ± 42.9	**0.006** [+]
p-ANCA (Elisa) (AU/mL)	7.5 ± 24.1	13.9 ± 33.1	0.509 [+]
CRP (mg/L)	104.4 ± 62.9	97.8 ± 71.7	0.592 [+]
ESR (mm/h)	81.7 ± 29.8	75.8 ± 30.8	0.384 [x]
e-Gfr (mL/min/1,73m^2)	66.6 ± 30.3	54.4 ± 36.0	0.164 [+]
Urea (mg/dL)	58.8 ± 56.3	89.5 ± 77.6	**0.029** [+]
Creatinine (mg/dL)	1.58 ± 1.56	2.48 ± 2.59	0.334 [+]
Uric acid (mg/dL)	5.23 ± 1.42	5.74 ± 2.66	0.783 [+]
Uric acid / creatinine ratio	5.07 ± 2.69	3.76 ± 2.35	**0.030** [+]
Total protein (g/dL)	6.52 ± 0.61	6.46 ± 0.79	0.707 [x]
Albumin (g/dL)	3.37 ± 0.52	3.55 ± 0.64	0.189 [x]
T.protein / Alb ratio	1.95 ± 0.20	1.86 ± 0.31	**0.027** [+]
AST (U/L)	27.8 ± 22.7	34.5 ± 50.6	0.100 [+]
ALT (U/L)	21.5 ± 23.3	46.0 ± 105.6	0.330 [+]
GGT (U/L)	47.2 ± 56.5	67.5 ± 110.9	0.993 [+]
ALP (IU/L)	76.2 ± 40.2	95.7 ± 55.6	**0.038** [+]
LDH (U/L)	226.7 ± 97.14	263.53 ± 145.52	0.171 [+]
Total biluribine (mg/dL)	0.46 ± 0.20	0.62 ± 0.79	0.349 [+]
Direct biluribine (mg/dL)	0.22 ± 0.11	0.29 ± 0.59	0.245 [x]
Haemoglobin (g/dL)	10.5 ± 2.23	10.4 ± 2.78	0.866 [x]
Haemotocrit (%)	31.6 ± 6.53	32.01 ± 8.63	0.813 [x]
MCV (fL)	91.3 ± 61.9	81.7 ± 5.17	0.408 [+]
Platelet (/μl)	370.8 ± 141.4	367.0 ± 172.4	0.812 [+]
WBCs (10e3/μL)	12.3 ± 4.25	10.6 ± 4.58	**0.046** [+]
Neu (10e3/μL)	9.68 ± 3.97	8.18 ± 3.99	0.094 [x]
Lym (10e3/μL)	1.18 ± 0.69	1.42 ± 0.68	0.077 [+]
Neu/Lym ratio	11.71 ± 8.69	8.08 ± 8.03	**0.016** [+]
BVAS	19.5 ± 7.10 (7-39)	16.5 ± 6.65 (7-31)	**0.047[x]**
Overall duration of disease (weeks)	230.2 ± 213.2	200.2 ± 171.7	0.658 [+]
Time to Mortality Post-Disease Onset (Weeks)	121.6±1 59.4	50.6 ± 51.8	0.457 [+]

c-ANCA: antineutrophil cytoplasmic autoantibody, cytoplasmic; p-ANCA: perinuclear anti-neutrophil cytoplasmic antibodies; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Gfr: glomerular filtration rate; AST: aspartate aminotransferase; ALT: alanine aminotransferase: GGT: gamma-glutamyl transferase; ALP: alkaline phosphatase; MCV: mean corpuscular volume; MPV: mean platelet volume; WBCs: white blood cells; Neu; neutrophil; Lym: lymphocyte; BVAS: Birmingham Vasculitis Activity Score.

Levene's test was used for homogeneity of variances, and Shapiro-Wilk test was used for normality.

[x] Independent simple t-test *p*-value, [+] Mann-Whitney U-test *p*-value.

Table II. Comparative analysis of demographic and laboratory parameters in in GPA patients according to Rf positivity status.

		Rf positives (n=37)	Rf negatives (n=45)	*p*-value*
Gender	Male	21 (51.2 %)	20 (48.8 %)	0.267
	Female	16 (39 %)	25 (61 %)	
ANCA (Ifa) (PR3 a/o MPO)	Positives	26 (44.1 %)	33 (55.9 %)	0.759
	Negatives	11 (47.8 %)	12 (52.2 %)	
c-ANCA (Elisa)	Positives	35 (53.8 %)	30 (46.2 %)	0.002
	Negatives	2 (11.8 %)	15 (82.2 %)	
p-ANCA (Elisa)	Positives	4 (36.4 %)	7 (63.6 %)	0.530
	Negatives	33 (46.5 %)	38 (53.5 %)	
Spot urine protein/creatinine ratio	Normal & mild	19 (44.2 %)	24 (55.8%)	0.252
	Moderate	4 (28.6 %)	10 (71.4 %)	
	Severe	14 (56.0 %)	11 (44.0 %)	
Rituximab Usage	Present	24 (60%)	16 (40%)	0.008
	Absent	13 (31%)	29 (69%)	
Cyclophosphamide usage	Present	24 (42.1%)	33 (57.9%)	0.407
	Absent	13 (52.0%)	12 (48.0%)	
MMF or AZA or MTX usage	Present	14 (35.0%)	26 (65.0%)	0.072
	Absent	23 (54.8%)	19 (45.2%)	

ANCA (Ifa): antineutrophil cytoplasmic antibodies (immunofluorescence assay); c-ANCA: antineutrophil cytoplasmic autoantibody; p-ANCA: perinuclear anti-neutrophil cytoplasmic antibodies; PR3: proteinase 3; MPO: myeloperoxidase; MMF: mycophenolate mofetil; AZA: azathioprine; MTX: methotrexate. * Chi-square test *p*-value.

fer significantly (p=0.759). However, c-ANCA (Elisa) positivity was significantly higher in the Rf+ group (53.8% *vs*. 46.2%, p=0.002), while *p*-ANCA showed no significant association (p=0.530). There was no significant difference in spot urine protein/creatinine ratio between groups (p=0.252).

In Rf+ GPA patients, the rituximab usage rate was 60% (n=24), whereas in Rf- patients, it was 40% (n=16), and this difference was found to be significantly higher in Rf+ patients (p=0.008). In terms of cyclophosphamide usage, the rate was 42.1% (n=24) in Rf+ patients and 57.9% (n=33) in Rf - patients, with no statistically significant difference observed (p=0.407). Regarding mycophenolate mofetil, azathioprine, methotrexate usage, the rate was 35.0% (n=14) in Rf+ patients and 65.0% (n=26) in Rf- patients, with the difference approaching statistical significance (p=0.072).

A comparative analysis of the clinical manifestations and outcomes in patients with GPA according to the status of Rf positivity is summarised in Table III.

Rf positivity was detected in 80.6% of GPA patients with arthritis, compared to 19.4% in those without arthritis (p<0.001). Radiographic imaging (plain x-rays of hands and feet) was performed in all Rf+ patients presenting with arthritis, and no cases of erosive changes consistent with RA were identified. Conversely, Rf positivity was observed in only 18.8% of patients with skin involvement, whereas 51.5% of those without skin involvement were Rf+ (p=0.018). Among GPA patients, Rf positivity was observed in 16.7% of those with ESRD and 50% of those without (p=0.032).

Additional clinical manifestations and outcomes in GPA patients by Rf positivity revealed no significant associations. Rf positivity was similar in nasal/paranasal disease (51.0% *vs*. 36.4%, p=0.191), glomerulonephritis (49.0% *vs*. 51.0%, p=0.363), pulmonary nodules (50.9% *vs*. 33.3%, p=0.133), and pulmonary haemorrhage (46.2% *vs*. 53.8%, p=0.898). Central nervous system (CNS) involvement (26.7% *vs*. 49.3%, p=0.112), mononeuritis multiplex (33.3% *vs*. 47.1%, p=0.374), retro-orbital disease (0% *vs*. 46.2%, p=0.498), episcleritis (50.0% *vs*. 44.9%, p=0.841), cardiac involvement (28.6% *vs*. 46.7%, p=0.358), and mesenteric involvement (33.3% *vs*. 46.1%, p=0.547) also showed no differences. Life/organ-threatening diseases (50.0% *vs*. 31.8%, p=0.143), mortality (30.0% *vs*. 50.0%, p=0.118), and hospitalisation for infection (55.6% *vs*. 37.0%, p=0.093) were similar.

Based on the results of the logistic regression analysis, the factors associated with ESRD development in GPA patients are presented in Table IV (Logistic Regression-Backward Stepwise (Wald)/constant: -1.76 OR: 0.17 p<0.001). In the univariate analysis, severe proteinuria (OR: 48.23, 95% CI: 5.709–407.446, p<0.001), creatinine levels at diagnosis (>1.2 mg/dL, OR: 1.50, 95% CI: 1.191–1.890, p<0.001), Rf positivity (OR: 0.200, 95% CI: 0.041–0.980, p=0.032), the presence of pulmonary haemorrhage (OR: 3.75, 95% CI: 1.063-13.285, p=0.032), and nasal-paranasal involvement (OR: 0.27, 95% CI: 0.076–1.015, p=0.043) were significantly associated with ESRD development. In the multivariate analysis, severe proteinuria (OR: 49.45, 95% CI: 4.047–604.269, p=0.002) and Rf positivity (OR: 0.08, 95% CI: 0.009–0.741, p=0.026) were identified as independent predictive factors.

Discussion

Rf is an autoantibody produced against IgG and serves as an important biomarker for diagnosing and managing autoimmune diseases. Rf is frequently positive in connective tissue diseases such as RA and SjS. Approximately 70-80% of RA patients, 50–60% of primary SjS patients, and 25–30% of systemic sclerosis patients exhibit Rf positivity. Additionally, low levels of Rf positivity may be observed in infections, malignancies, and with advancing age. In GPA, Rf positivity is generally lower, ranging between 10–30% (11-13). In our retrospective single-centre cohort study evaluating the prevalence and clinical implications of Rf positivity in patients with GPA, several key findings emerged. Rf positivity was detected in 45.1% of GPA patients, of whom 35% (13 individuals) had low-positive Rflevels according to the ACR/EULAR 2010 classification criteria, yielding a

Table III. Comparative analysis of clinical manifestations and outcomes in GPA patients according to Rf positivity status.

		Rf positives (n=37)	Rf negatives (n=45)	*p*-value
Glomerulonephritis	Present	25 (49.0%)	26 (51.0%)	0.363*
	Absent	12 (38.7%)	19 (61.3%)	
Arthritis	Present	25 (80.6%)	6 (19.4%)	**<0.001***
	Absent	12 (23.5%)	39 (76.5%)	
Pulmonary haemorrhage	Present	12 (46.2%)	14 (53.8%)	0.898*
	Absent	25 (44.6%)	31 (55.4%)	
Meningeal involvement	Present	2 (100%)	0 (0.0%)	0.201**
	Absent	35 (43.8%)	45 (56.2%)	
CNS involvement	Present	4 (26.7%)	11 (73.3%)	0.112*
	Absent	33 (49.3%)	34 (50.7%)	
Retro-orbital disease	Present	0 (0.0%)	2 (100.0%)	0.498**
	Absent	37 (46.2%)	43 (53.8%)	
Cardiac involvement	Present	2 (28.6%)	5 (71.4%)	0.358*
	Absent	35 (46.7%)	40 (53.3%)	
Mesenteric involvement	Present	2 (33.3%)	4 (66.7%)	0.547*
	Absent	35 (46.1%)	41 (53.9%)	
Mononeuritis multiplex	Present	4 (33.3%)	8 (66.7%)	0.374*
	Absent	33 (47.1%)	37 (52.9%)	
Nasal&paranasal disease	Present	25 (51.0%)	24 (49.0%)	0.191*
	Absent	12 (36.4%)	21 (63.6%)	
Skin involvement	Present	3 (18.8%)	13 (81.3%)	**0.018***
	Absent	34 (51.5%)	32 (48.5%)	
Myositis	Present	1 (50.0%)	1 (50.0%)	0.888*
	Absent	36 (45.0%)	44 (55.0%)	
Non-cavitating pulmonary nodules	Present	28 (50.9%)	27 (49.1%)	0.133*
	Absent	9 (33.3%)	18 (66.7%)	
Episcleritis	Present	2 (50.0%)	2 (50.0%)	0.841*
	Absent	35 (44.9%)	43 (55.1%)	
ESRD	Present	2 (%16,7)	10 (%83,3)	**0.032***
	Absent	35 (%50)	35 (%50)	
Life/organ threatening diseases	Present	30 (50.0%)	30 (50.0%)	0.143*
	Absent	7 (31.8%)	15 (68.2%)	
Mortality	Present	6 (30.0%)	14 (70.0%)	0.118*
	Absent	31 (50.0%)	31 (50.0%)	
Infection requiring hospitalisation	Present	20 (55.6%)	16 (44.4%)	0.093*
	Absent	17 (37.0%)	29 (63.0%)	

ESRD: end-stage renal disease. *Chi-square test *p*-value.**Fisher's test *p*-value.

cumulative Rf+ GPA prevalence of 4.9 per 100,000 in a population of 750,000. This higher prevalence compared to the reported range may be due to regional or population-specific factors, such as genetic predispositions and environmental influences, or variations in laboratory methods (14).

While demographic features such as age and gender distribution, as well as overall disease duration, were similar between groups, distinct differences in laboratory and clinical parameters were identified.

In the present study, c-ANCA (Elisa) levels, total protein-to-albumin ratio, WBC counts, NLR, and BVAS were observed to be notably elevated in Rf+ patients. Our findings suggest that Rf+ GPA patients exhibit a higher inflammatory response and immune activation compared to Rf- GPA patients. The literature indicates that NLR is utilised as an indicator of inflammatory activity in autoimmune diseases, is effective in predicting renal prognosis in GPA patients, and demonstrates predictive properties for overall mortality in inflammatory conditions (15, 16). The higher c-ANCA (Elisa) levels and positivity rates observed in Rf+ GPA patients in our study may indicate increased disease severity (17). Additionally, the elevated serum total protein-to-albumin ratio observed in Rf+ GPA patients reflects the strength of the immune response in this patient group. Evidence suggests that it impacts mortality prediction in AAV and to affect prognosis in rheumatologic diseases (18-20). Rf is known to enhance immune complex formation, leading to endothelial dysfunction, pro-inflammatory cytokine release, and progressive vascular damage. Moreover, these immune complexes are reported to trigger endothelial activation and initiate pro-inflammatory processes (21, 22). In this context, the increased WBC counts, NLR, elevated serum total protein-to-albumin ratio, higher c-ANCA (Elisa) levels/positivity rates and BVAS observed in our study may represent an indication of Rf-mediated immune complex-driven pro-inflammatory effects.

In our study, urea levels were observed to be markedly reduced in Rf+ GPA patients, whereas the decline in mean creatinine levels was not statistically significant. Additionally, the prevalence of ESRD was lower in the Rf+ group, while rituximab usage was notably more frequent in this group; the use of other immunosuppressive agents did not show any significant differences. The lower prevalence of ESRD in Rf+ GPA patients in our study may reflect differences in patterns of organ involvement or immune mechanisms. This notion aligns with recent evidence suggesting that distinct serological and inflammatory profiles may delineate prognostically relevant phenotypes within the AAV spectrum (23). Similar trends have been reported in previous studies, which indicate that Rf positivity correlates with a unique clinical phenotype in AAV and may potentially influence renal prognosis (24, 25).

The higher rate of rituximab usage in Rf + GPA patients, who exhibited elevated inflammatory markers, aligns

Table IV. Logistic regression analysis to predict the development of ESRD in GPA patients.

Dependent variable	Univariate				Multivariate			
	OR	95% CI		*p*	OR	95% CI		*p*
		Lower	Upper			Lower	Upper	
Gender (male/female)	0.47	0.123	1.618	0.211				
RF status (negative or positive)	0.200	0.041	0.980	**0.032**	0.08	0.009	0.741	**0.026**
Proteinuria (normal & moderate or severe)	48.23	5.709	407.446	**<0.001**	49.45	4.047	604.269	**0.002**
Pulmonary haemorrhage (absent or present)	3.75	1.063	13.285	**0.032**				
Nasal-paranasal involvement (absent or present)	0.27	0.076	1.015	**0.043**				
Life organ involvement (absent or present)	1.25	1.101	1.419	0.023				
Creatinine levels (≤1.2 mg/dl or >1.2 mg/dl)	1.50	1.191	1.890	**<0.001**				

Logistic Regression-Backward Stepwise (Wald)/constant: -1.76 OR: 0.17 $p<0.001$. CI: confidence interval; OR: odds ratio.

with evidence supporting rituximab as a superior therapeutic option for inducing and maintaining remission in AAV, particularly in patients with relapsing or refractory disease (26, 27). Furthermore, rituximab has demonstrated a stronger correlation with improved treatment response rates in Rf+ RA patients (28). In light of this information, the higher rate of rituximab usage in Rf+ GPA patients and its potentially greater efficacy in this group may explain the observed lower rates of ESRD development.

The elevated ALP levels observed in Rf- GPA patients in this study may reflect underlying renal pathology. Consistently, previous studies have linked increased ALP to aggressive or extensive renal involvement and progression toward ESRD in patients with chronic kidney disease (CKD) not yet on dialysis. (29). Additionally, elevated ALP has been linked to renal hyperfiltration and subsequent glomerular injury, as well as kidney function decline in patients with nephrotic-range proteinuria (30, 31). Consequently, the lower ALP levels identified in Rf+ GPA patients in our study, coupled with the lower rates of ESRD, appear consistent with the literature.

Within the present study, the higher uric acid-to-creatinine ratio observed in Rf + GPA patients could be considered consistent with previous mechanisms linking systemic inflammation to metabolic alterations (32, 33). Enhanced purine turnover and impaired renal clearance due to systemic inflammation may explain the elevated uric acid-to-creatinine ratio observed in Rf+ GPA patients. Higher c-ANCA levels, WBC counts, NLR, and BVAS in this group reflect intensified inflammatory and immunological activity, which may further contribute to altered uric acid metabolism (34).

In this study, Rf positivity was strongly associated with arthritis in GPA patients, potentially through immune complex formation, complement activation and sustained inflammation. This aligns with evidence from RA, where Rf is linked to more severe joint involvement and worse prognosis. A similar association has been reported in cryoglobulinaemic vasculitis, particularly with pulmonary involvement, where Rf predicts poorer outcomes (35-37). In the context of GPA, the fact that Rf positivity contributes to the arthritis phenotype suggests that this autoantibody may be an important biomarker in identifying different clinical subgroups in GPA. Furthermore, the observation of an arthritis-dominant phenotype in Rf+ patients suggests that it would be rational to question GPA in patients presenting with Rf+, ANA (Ifa) and anti-ccp negative arthritis.

In our cohort, none of the Rf+ GPA patients fulfilled the clinical or radiographic diagnostic criteria for RA at baseline or during subsequent follow-up. Additionally, anti-CCP positivity was detected in only one patient, and radiographic evaluation of the hands and feet revealed no erosive joint disease either initially or throughout the observational period. While recent studies indicate that AAV can indeed emerge in patients previously diagnosed with RA, this clinical pattern typically involves distinct serological profiles, such as MPO-ANCA positivity, along with characteristic clinical features including erosive arthritis and ocular manifestations (38). The absence of hallmark RA features in our GPA cohort does not support a true RA-AAV overlap syndrome. Conversely, elevated Rf levels in these patients may not indicate coexisting RA, but rather reflect non-specific immune activation. Nevertheless, given the limited sample size of our study, the possibility of subclinical or evolving RA in Rf+ GPA patients cannot be definitively excluded. Therefore, clinicians should remain vigilant and consider periodic reassessment for potential RA features during long-term clinical follow-up.

In addition, our analyses revealed that Rf positivity was associated with a lower frequency of skin involvement in the Rf+ GPA group. Although Rf has traditionally been linked to extra-articular manifestations in RA its direct association with cutaneous findings remains controversial (36, 39). A multicentre cohort study demonstrated that skin involvement was observed in only 12.8% of Rf(+)/ANCA(+) patients, whereas it was significantly more common in Rf(+)/ANCA(-) and Rf(-)/ANCA(-) subgroups (60.0% and 48.0%, respectively; $p<0.001$) (25). Another retrospective analysis reported a numerically higher rate of cutaneous manifestations

in Rf+ AAV patients compared to Rf- ones (28% *vs*. 11%), although the difference was not statistically significant (24). These findings suggest that the inverse association between Rf positivity and skin involvement in GPA may reflect a distinct serological phenotype, which might not extend to other AAV subgroups. This interpretation is supported by evidence that ANCA-defined AAV subsets exhibit differing patterns of organ involvement and clinical behaviour (23, 37, 38).

Conclusion

In conclusion, Rf+ GPA patients show increased inflammatory and immune activity with high c-ANCA levels, WBC counts, NLR, serum total protein/albumin ratio, and BVAS. This may suggest that Rf-mediated immune complex formation could influence disease severity and organ involvement patterns by triggering vascular and systemic inflammation. Furthermore, the lower ESRD rates and higher rituximab use in Rf+ GPA patients suggest a distinct clinical phenotype, potentially associated with better renal outcomes. Logistic regression analysis highlights significant factors associated with ESRD development in GPA patients, including severe proteinuria, creatinine levels >1.2 mg/dL at diagnosis, Rf positivity, pulmonary haemorrhage, and nasal-paranasal involvement, with severe proteinuria and Rf positivity emerging as independent predictive factors. The fact that an arthritis-dominant phenotype is more frequent in Rf+ GPA patients and inversely associated with skin involvement further suggests that Rf may influence clinical features and disease course in GPA. Rf positivity stands out as an important biomarker determining the disease phenotype and immune activity in GPA patients. In this context, further studies are needed to better understand the effects of Rf positivity on GPA.

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