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Original Article

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Clinical Features and Outcomes of Patients with Granulomatosis with Polyangiitis and Review of Literature

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Abstract

Objective: Granulomatosis with polyangiitis (GPA) is a type of antineutrophil cytoplasm antibody-associated vasculitis. This study aimed to investigate the clinical and laboratory findings of patients with GPA and to determine which factors were associated with poor prognosis and renal outcome.
Materials and Methods: Medical records of patients diagnosed with GPA between 2000 and 2014 were retrospectively analyzed.
Results: A total of 53 patients (60.4% men) with a mean age at diagnosis of 47.1±16.3 years were included in this study. The median baseline serum creatinine (SCr) level was 1 (interquartile range [IQR], 0.76-2.95) mg/dL. Renal involvement was detected in 63.5% of the patients. Patients with renal involvement had less ear-nose-throat involvement (p=0.002) and lower hematocrit levels (p=0.001). The 1-year, 5-year, and 10-year death-censored renal survival rates were 93.3%, 81.4%, and 63.4%, respectively. There were 15 deaths (28.3%) in this series, and the median patient survival after diagnosis was 51 (IQR, 20-109.5) months. Age ≥65 years and SCr level ≥1.4 mg/dL at diagnosis were retained as the independent predictors of mortality.
Conclusion: Survival of patients with GPA is closely associated with age and renal function at admission. The delay in diagnosis could have influenced the development of irreversible kidney damage, one of the significant determinants of mortality.
Keywords: Vasculitis, granulomatosis with polyangiitis, mortality, renal insufficiency

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INTRODUCTION

Granulomatosis with polyangiitis (GPA) is a type of antineutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) typically associated with necrotizing, granulomatous inflammation (1, 2). This rare systemic disease predominantly affects the upper respiratory tract, lungs, and kidneys. The kidneys are affected in approximately 70% of the patients with GPA, and renal involvement has been reported as a significant factor in the treatment and prognosis (3-5).

Several investigators have analyzed the impact of vasculitis and demographic features at the time of diagnosis on mortality among patients with GPA (6-10). However, there are few studies elaborating on renal survival and the impact of renal involvement on the overall survival in patients with GPA. Series with GPA from Turkey have also been rarely reported (11, 12).

In this study, we aimed to investigate the clinical characteristics and laboratory findings of our patients with GPA and to determine which factors were associated with poor prognosis and renal outcome in these patients.

MATERIALS AND METHODS

Study Design and Population

We conducted a retrospective study of 53 patients with GPA who were diagnosed between 2000 and 2014 and were followed in the Divisions of Rheumatology and Nephrology of Cerrahpaşa School of Medicine, İstanbul, Turkey. Patients ≥18 years at diagnosis who met the

American College of Rheumatology classification criteria for GPA were included (13).

Data on demographic and clinical manifestations, laboratory findings, histopathology, disease course, follow-up time, treatments, adverse events, and outcomes were obtained and recorded from patients' files. The following data were collected for baseline evaluation: age at diagnosis; gender; smoking status (grouped as smokers-current/quitters and never-smokers); time from first symptoms attributable to GPA to diagnosis; laboratory data, including white blood count, hemoglobin, hematocrit (Htc), serum creatinine (SCr) level, serum albumin level, urinalysis for urine protein, red blood cell count and casts, 24-hour urine protein excretion, C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), and ANCA serology. Type of ANCA was categorized as proteinase 3 ANCA (PR3-ANCA) if there was positivity by PR3-ANCA by enzyme-linked immunosorbent assay (ELISA) or a cytoplasmic ANCA (c-ANCA) pattern by indirect immunofluorescence microscopy (IIF) and as myeloperoxidase ANCA (MPO-ANCA) if there was positivity by MPO-ANCA by ELISA or perinuclear ANCA (p-ANCA) pattern by IIF. Types of organ involvement during the disease course were recorded.

Details about the use of glucocorticoids (GCs) and/or other immunosuppressive agents during follow-up were also collected. Patients who received at least 1 intravenous (IV) dose of cyclophosphamide (CYC) or 1 month of oral CYC were considered to have been treated with CYC. Patients who had received at least 1 infusion of rituximab (RTX) were considered to have been treated with RTX.

Definitions

Renal involvement was defined as the presence of hematuria >10 red blood cells/hpf and/or proteinuria >1+ or ≥500 mg/day and/or serum creatinine ≥1.41 mg/dL and/or rise in creatinine >30%, or creatinine clearance fall >25%, attributable only to vasculitis per the Birmingham Vasculitis Activity Score (version 3) form, excluding the other causes (14). The histopathological diagnosis of kidney confirming GPA was also considered as renal involvement.

Chronic kidney disease was defined according to the kidney disease: improving global outcomes guidelines (15). The estimated glomerular filtration rate (eGFR) was calculated using the chronic kidney disease epidemiology collaboration formula (16). Rapidly progressive glomerulonephritis (RPGN) was defined as progressive loss of renal function over a comparatively short period of time (days, weeks, or months) with features of glomerular disease in the urinalysis (17). End-stage renal disease (ESRD) was defined as eGFR <15 mL/min/1.73 m^2, initiation of dialysis, or renal transplantation.

Histopathological classification was based on the percentage of normal glomeruli; cellular crescents; or global sclerotic glomeruli: focal, crescentic, mixed, and sclerotic. The focal category is defined by the presence of more than 50% of normal glomeruli, the crescentic category by more than 50% of glomeruli with cellular crescents, the mixed category by less than 50% of normal glomeruli and crescentic or sclerotic lesions, and the sclerotic category by more than 50% of glomeruli with global sclerosis (4).

Complete remission was defined as disappearance of clinical disease activity and stabilization or improvement of renal function. In partial remission, there was a clear suppression of disease with stabilization of the renal function and at least partial resolution of the pulmonary infiltrates, and disease in other organs was required to show the signs of improvement. Resolution of hematuria was also a criterion for remission, but persistent proteinuria was considered as the consequence of glomerular damage. Patients who remained dialysis dependent were considered to be in remission if the extrarenal manifestations and the hematuria had completely ceased. Relapse was defined as recurrence of the presenting symptoms or appearance of a new organ involvement attributable to GPA (18). Damage was defined as a non-healing scar which would not respond to immunosuppressive therapy. The presence of complete remission, partial remission, relapse, and damage status was evaluated at the last visit.

Assessment of Disease Stages and Activity, Extent of Disease, and Mortality

The disease severity of each patient was classified as "non-organ threatening disease" or "organ-threatening/life-threatening disease" according to the European League Against Rheumatism/European Renal Association-European Dialysis and Transplant Association recommendations for the management of AAV (19).

We followed up the patients included in this study from the date of diagnosis until occurrence of death, loss to follow-up, or April 2014, whichever occurred first. Follow-up time was defined as the time from diagnosis to the last visit in our center. For the analysis of patient survival and renal survival, the censoring date was the last telephonic interview before April 2014. Survival time was calculated from the date of diagnosis and ended on the date of censoring or at the time of death. Renal survival was

Main Points

- ANCA was negative in 7.5% of the patients with GPA: this emphasizes the importance of histopathology and clinical evaluation in GPA diagnosis.
- Age ≥ 65 years and SCr level ≥ 1.4 mg/dL at admission were retained as the independent predictors of mortality.
- Vasculitis is a multi-systemic disease; early referral to nephrology from other departments is important.
- The delay in diagnosis could have influenced the development of irreversible kidney damage and poor patient prognosis.

defined as preserved renal function (no need for renal replacement therapy [RRT]).

Treatment Protocols

Therapeutic regimens varied between patients depending on the disease severity and changes in the standard of treatment over the years. CYC (oral [2 mg/kg body weight/day] or pulse [15 mg/kg body weight every 3 or 4 weeks]), with adjustment according to renal function and age, was mostly used for remission induction. The treatment was combined with IV methylprednisolone (MP) (mainly pulse 500-1,000 mg/day for 3 consecutive or alternate days) and subsequent gradual decline until reaching a dose of 15 mg/day after 3 months. Methotrexate (MTX) (0.3 mg/kg body weight/week) combined with oral steroids could also be used for remission induction. All the patients using CYC (oral or intravenous) received uroprotection with 2-mercapto ethanesulfonate sodium. Trimethoprim/sulfamethoxazole was administered to some patients receiving the combination of GCs and CYC for *Pneumocystis jiroveci* pneumonia prophylaxis. CYC dosages were defined as the cumulative doses (mg) that were administered to the patient during the disease course.

Maintenance treatment included MTX (up to 25 mg/week) or azathioprine (AZA) (2-3 mg/kg/day) or mycophenolate mofetil (MMF) (1,000-2,000 mg/day) for at least 24 months, along with a dose of prednisolone between 2.5 and 7.5 mg/day.

Treatment protocols, including RTX as induction therapy and/or maintenance therapy, were also recorded. RTX use in GPA started in our center in 2008. RTX was administered according to 2 separate dosing regimens depending on physician reference; 1 g of RTX on days 1 and 15 or 375 mg/m^2 body surface area weekly for 4 weeks.

Some patients with severe alveolar hemorrhage or RPGN received additional plasma exchange. The patients requiring hemodialysis were recorded. Permanent organ damage was recorded at the last visit.

Statistical Analysis

Categorical data were summarized as percentages; significant differences or associations were analyzed using the chi-squared test. Continuous variables were presented as mean±standard deviation (SD) or median and interquartile range (IQR), depending on normality demonstrated by the Kolmogorov-Smirnov normality test. Associations were analyzed using the independent sample t-test or Mann-Whitney U test, when appropriate. We used the Kaplan-Meier method to analyze survival and to compare the differences in the survival between clinical variables, estimating the statistical significance using the log-rank method of Mantel-Haenszel. For mortality analyses, independent variables that appeared to have statistical significance in the univariate analysis were included in a multivariate logistic regression model using a backward stepwise method. The odds ratios (OR) and their 95% confidence interval (CI) obtained in the adjusted regression analysis were calculated. All the tests were performed using the Statistical Package for the Social Sciences for Windows version 17.0 software (SPSS Inc.; Chicago, IL, USA). A p value <0.05 was considered statistically significant.

This study was approved by the Ethics Committee of Cerrahpaşa School of Medicine, İstanbul University-Cerrahpaşa, (Approval Date: September 04, 2012; Approval Number: 26694). The study was in adherence with the Helsinki Declaration of 1975 (as revised in 1983). Informed consent was obtained from the patients who participated in this study.

RESULTS

A total of 53 patients (60.4% men) were included in this study. The mean age of the patients at diagnosis was 47.1±16.3 years, and 17% of patients were older than 65 years at disease onset. The median time from the first symptoms to diagnosis was 3.5 (IQR, 1-12) months. The median baseline SCr level was 1 (IQR, 0.76-2.95) mg/dL and the median baseline eGFR level was 84.7 (IQR, 15.9-103.4) mL/min/1.73m^2. ESR and CRP values were increased in more than 75% of the patients at diagnosis. ANCA was detected in 49 patients (92.5%) at diagnosis of which 43 patients (81.1%) had a c-ANCA, whereas 8 (17.8%) had a p-ANCA pattern. ANCA negativity occurred in 7.5% of the patients. Anti-MPO antibodies on ELISA were present in 12 of the 46 patients (26.1%), whereas anti-PR3 antibodies were present in 30 of the 44 patients (68.2%). The baseline demographic, clinical, and laboratory data are summarized in Table 1.

A total of 40 patients (75.5%) were classified as having "organ-threatening/life-threatening disease" and 13 patients (24.5%) as having "non-organ threatening disease." Nonspecific symptoms such as fever, fatigue, and weight loss were present in over 50% of the patients. Pulmonary involvement was present in 39/53 (73.6%) of the patients, most commonly presenting with nodules/cavities (29/39, 74.3%) and frosted glass areas (10/39, 25.6%). Two patients had alveolar hemorrhage, and 1 patient had an endobronchial lesion. Ear-nose-throat (ENT) involvement manifesting as sinusitis, hearing loss, or bloody nasal crusts was found in 33/53 (62.3%) patients. Renal involvement was detected in 33/52 (63.5%) patients, hematuria (26/33, 78.8%) and proteinuria (20/33, 60.6%) being the most common findings. Renal failure (SCr level ≥1.4) at diagnosis was present in 18/53 (33.9%) patients. Ophtalmic involvement described as conjunctivitis, episcleritis, uveitis, scleritis, or retro-orbital mass was detected in 15/53 (28.3%) patients. Skin involvement manifesting as purpura, rash, or nodules was found in 14/53 (26.4%) patients. Neurological involvement was seen in only 5 (9.4%) patients.

The diagnosis of GPA vasculitis was supported by histopathology in 33 (62.3%) patients on the basis of the biopsy samples obtained from mainly the kidney, cutaneous lesions, and lung. Of these, 2 biopsies were classified as crescentic, 3 as sclerotic, and 1 as mixed AAV glomerulonephritis. Two renal biopsy

Table 1. Demographic, clinical, and laboratory data at baseline in study patients

Variable	Results
Age at diagnosis, years	47.1±16.3
Men, n (%)	32 (60.4)
Time from first symptoms to diagnosis, months	3.5 (1-12)
Smokers, n (%)	21 (39.6)
Leukocytes, $\times 10^9$/L	9.6±4.1
Hematocrit, %	35.6±6.0
Serum creatinine, mg/dL	1.0 (0.76-2.95)
Serum albumin, g/L (n=46)	3.2±0.7
eGFR, mL/min/1.73 m^2	84.7 (15.9-103.4)
Proteinuria, mg/day	270 (103.5-1,540.8)
Erythrocyte sedimentation rate, mm/h (n=50)	66.5±34.4
C-reactive protein, mg/dL (n=52)	43.8 (5.8-100.1)
Positive, n (%) (n=49)	
c-ANCA, n (%)	43 (81.1)
p-ANCA, n (%)	8 (17.4)
Anti-MPO positivity, n (%) (n=46)	12 (26.1)
Anti-PR3 positivity, n (%) (n=44)	30 (68.2)
ANCA negativity, n (%)	4 (7.5)

eGFR: estimated glomerular filtration rate; c-ANCA: cytoplasmic antineutrophil cytoplasm antibody; p-ANCA: perinuclear antineutrophil cytoplasm antibody; MPO: myeloperoxidase; PR3: proteinase 3

findings could not be obtained from the medical records. In the remaining patients, the diagnosis was made according to the clinical evaluation in conjunction with a positive ANCA-test.

In Table 2, we compare the clinical characteristics between patients with and without renal involvement. The patients with renal involvement had less ENT involvement (p=0.002) and lower baseline Htc levels (p=0.001). Patient survival was significantly lower in patients with GPA and with renal involvement than in patients with GPA and without renal involvement (39 [17-87] months versus 105 [39-129] months, p=0.008). ANCA positivity was detected in 30/33 (90.9%) patients with renal involvement, 26/33 (78.8%) had c-ANCA pattern, and 5/28 (17.9%) had p-ANCA, whereas ANCA was detected in 18/19 (94.7%) without renal involvement, 16/19 (82.2%) had c-ANCA pattern and 3/17 (17.6%) had p-ANCA pattern. Renal involvement was seen in 3 patients without ANCA positivity.

The median follow-up time in our center was 26 (IQR, 10-82) months. IV MP (3-5 consecutive pulses) was administered to 41 (77.4%) patients with severe disease. For induction therapy, 48 (90.6%) patients received CYC (oral daily 4/48), 3 (5.7%) received MTX, and 2 (3.8%) received RTX. Maintenance therapy primarily included AZA in 27 (50.9%) patients, MTX in 7 (13.2%) patients, and MMF in 2 (3.8%) patients. RTX was additionally used as a secondary agent in 14 (26.4%) patients of remission induction after they did not respond or had relapse with CYC or for remission maintenance. The median cumulative CYC dose per patient was 6 (IQR, 3-12.8) g. Only 3 patients received a cumulative dose of CYC of more than 50 g.

At the last visit, 20 (37.7%) patients achieved complete remission, 24 (45.3%) had partial remission, and 9 (17%) had relapses. During the disease course, 18 (34%) patients experienced 1 or more disease relapses with a mean rate of 1.3±0.7. Skin and lung involvement were mostly seen in the patients with relapses compared with the patients without relapses (p=0.03 and p=0.02, respectively). The patients with relapses received RTX more than the patients without relapses (66.7% vs. 22.2%, p=0.004) (excluding the patients who were followed up before 2008). There were no significant differences in other demographic, clinical, and laboratory data between the patients with and without relapses (data not shown).

Plasma-exchange therapy was administered to 5 patients with RPGN, 1 with accompanying alveolar hemorrhage.

Major infections were documented in 9 patients: cytomegalovirus pneumonia in 2 patients, *Pseudomonas aeruginosa* pneumonia in 2, fungal pneumonia in 1, liver hydatid cyst in 1, skin tuberculosis in 1, tuberculosis menengitis in 1, and spondylodiscitis in 1.

In this study, we observed renal cell carcinoma in 1 patient who received a total of 6 g CYC dosage, and he achieved remission after surgery.

Permanent organ damage occurred in several patients. Organ damage manifested mainly as dyspnea (75.5%), cutaneous ulcers (25%), cosmetic and functional nasal deformities (13.2%), and hearing loss (7.5%).

Renal Survival

A total of 11 patients (20.8%) required hemodialysis until the censoring date; 1 of them had temporary hemodialysis, and another had preemptive renal transplantation. The median time for permanent RRT onset was 8 (IQR, 1-28) months.

The median renal survival time after diagnosis was 39 (IQR, 13-101.5) months. The 1-year, 5-year, and 10-year death-censored renal survival rates were 93.3%, 81.4%, and 63.4%, respectively

Table 2. Comparison of clinical characteristics of patients with GPA with and without renal involvement

Variable	GPA with renal involvement** (n=33)	GPA without renal involvement** (n=19)	p
Age, years*	50 (32-62.5)	44 (30-60)	0.842
Male, n (%)	20 (60.6)	12 (63.2)	0.855
Pulmonary involvement, n (%)	27 (81.8)	11 (57.9)	0.061
ENT involvement, n (%)	15 (45)	17 (89.5)	0.002
Hematocrit, %*	33.5 (28.1-38.6)	38.9 (36.3-42.6)	0.001
Serum albumin, g/L* (n=45)	3.1 (2.7-3.7)	3.3 (2.9-4)	0.096
Erythrocyte sedimentation rate, mm/h* (n=49)	66.5 (46.8-100.5)	52 (25-82)	0.119
CRP, mg/dL* (n=51)	46 (7-115.5)	20 (3.3-90)	0.173
ANCA positivity, n (%)*	30 (90.9)	18 (94.7)	0.618
Positive, n (%) (n=45)			
c-ANCA, n (%)*	26 (78.8)	16 (84.2)	0.633
p-ANCA, n (%)*	5 (17.9)	3 (17.6)	0.986
PR-3 level, IU/mL* (n=43)	20.7 (4.2-94)	6.8 (3.3-47.2)	0.243
MPO level, IU/mL* (n=45)	1.7 (0.6-2.9)	1.6 (0.3-9.1)	0.943
Mortality, n (%) (n=49)	11 (35.5)	3 (16.7)	0.160
Patient survival, months (n=49)	39 (17-87)	105 (39-129)	0.008

*Data were obtained at diagnosis
**In 1 patient, renal involvement could not be evaluated because of missing data
GPA: granulomatosis with polyangiitis; ENT: ear-nose-throat; c-ANCA: cytoplasmic antineutrophil cytoplasm antibody; p-ANCA: perinuclear antineutrophil cytoplasm antibody; MPO: myeloperoxidase; PR3: proteinase 3; CRP: C-reactive protein

(Figure 1); the 1-year, 5-year, and 10-year non-death-censored renal survival rates were 79.9%, 66.1%, and 46.4%, respectively (Figure 2).

Patient Survival

The median patient survival was 51 (IQR, 20-109.5) months. There were 15 deaths (28.3%) during this study. Three patients were lost to follow-up after a mean duration of 8.1±3.6 months after diagnosis, 1 was in complete remission, and 2 patients were in partial remission at the time of their last clinical visit. A total of 11 patients died within 1 year. No deaths were observed during complete remission periods. Eleven patients died during the partial remission period and 4 during relapses. The cause of death included pneumonia (n=3), cerebrovascular diseases (n=3), pulmonary thromboembolism (n=1), alveolar hemorrhage (n=1), and unknown (n=7). The 1-year, 5-year, and 10-year patient survival rates were 86%, 73.1%, and 61.9%, respectively (Figure 3).

Factors associated with death in the univariate analysis and multivariate analysis are listed in Table 3. Univariate analysis showed the following baseline variables as predictors of poor prognosis: age ≥65 years and SCr level ≥1.4 mg/dL. Age ≥65 years and SCr level ≥1.4 mg/dL were retained as the independent predictors of mortality ([OR=0.147, 95% CI: 0.023-0.960, p=0.045] and [OR=0.213, 95% CI: 0.051-0.863, p=0.033], respectively) in the multivariate analysis. Figure 4 shows the long-term survival analyses according to the presence of baseline SCr level ≥1.4 mg/dL.

DISCUSSION

We determined the clinical characteristics of patients with GPA focusing on the renal involvement and renal survival on the basis of a cohort from Turkey. Different studies in the literature have different follow-up periods and study populations, resulting in some clinical discrepancy among them.

GPA seems to affect a relatively younger population in Turkey compared with other cohorts (2, 20-24). The male predilection has been reported to be similar to other large cohorts (2, 20-22, 24). In contrast, some cohorts have reported a female predomi-

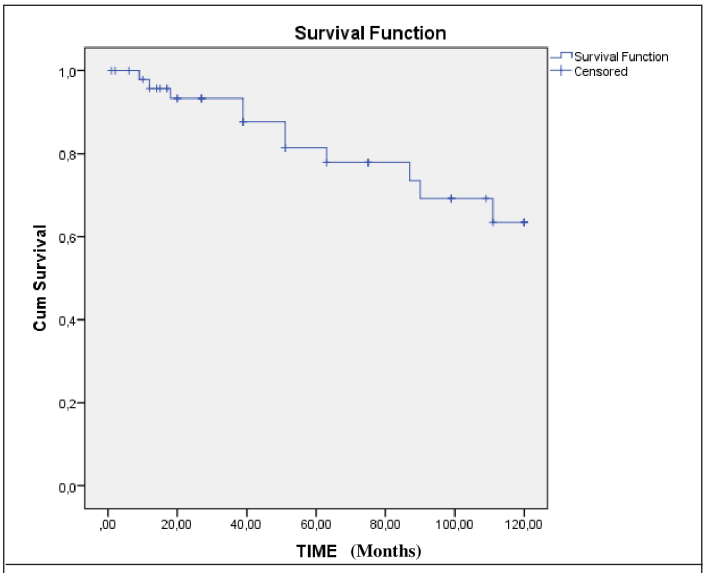

Figure 1. Death-censored renal survival analyses

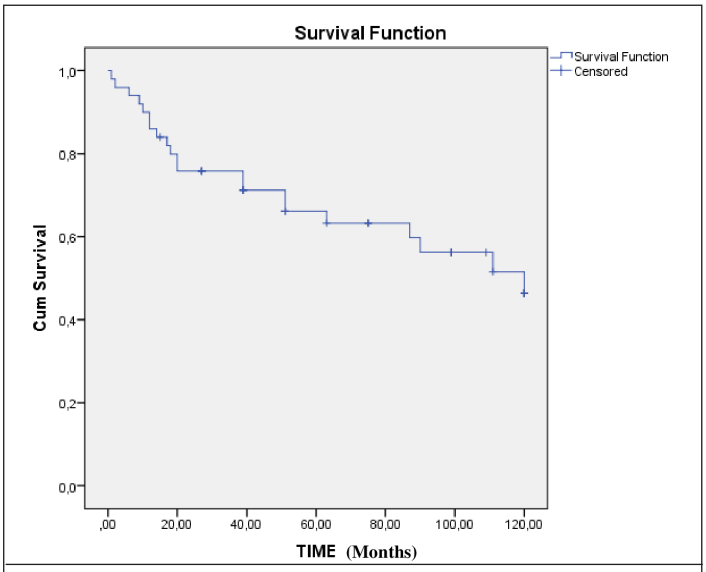

Figure 2. Non-death-censored renal survival analyses

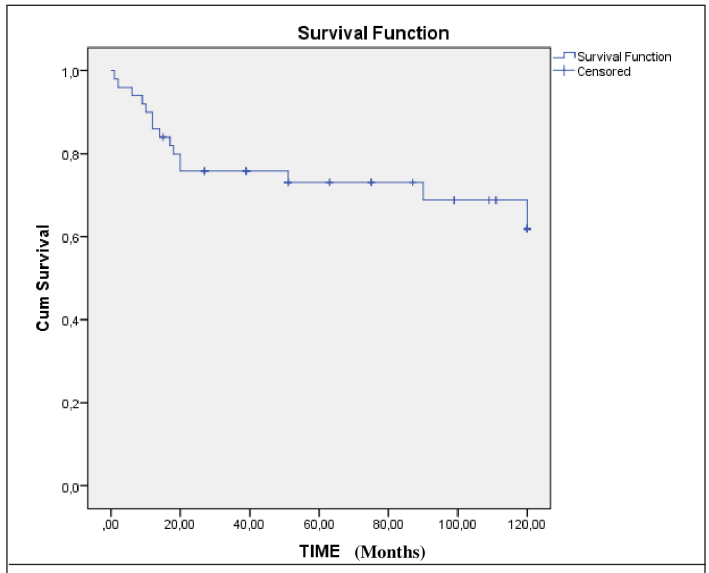

Figure 3. Patient survival analyses

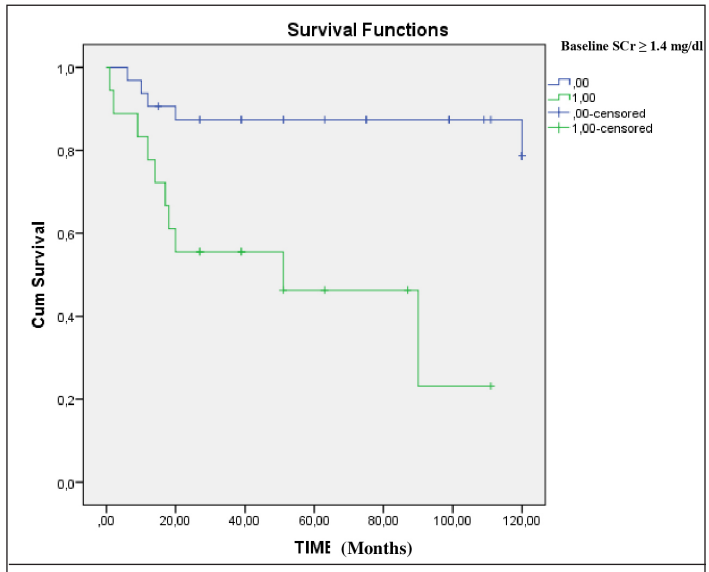

Figure 4. Long-term patient survival analyses for patients with granulomatosis with polyangiitis on the basis of baseline serum creatinine level ≥1.4 mg/dL (p=0.001)

nance (23, 25, 26). In our study, 40 patients (75.5%) were classified as having "organ-threatening/life-threatening disease" and 13 patients (24.5%) as having "non-organ threatening disease." This is similar to the patient population of Wegener's Granulomatosis Etanercept Trial classified as limited or severe (27).

As already described, the most common symptoms were nonspecific (fever, fatigue, joint pain, and weight loss) (20-25). Organ involvements were pulmonary, renal, and ENT in our study. The positivity rate for c-ANCA in our data was identical to that of other studies (21, 24, 26-28), and p-ANCA positivity rate was similar to that of some studies (20, 22, 25) and ranged between 12% and 17.5%. ANCA was negative in 7.5% of the patients with GPA. This emphasizes the importance of histopathology and clinical evaluation in GPA diagnosis. In this study, diagnosis of vasculitis was supported by the histopathological findings in 62.3% of the cases. This percentage was less than that seen in other cohorts (20, 29) but higher than that in the study by Orden et al. (21).

The renal outcome in patients with GPA changes according to the clinical characteristics of the study populations and the different criteria defining the renal involvement in different nephrology units. Renal involvement was observed in 63.5% of our patients with GPA. Studies comparing the patients with GPA with and without renal involvement have been rarely reported (5, 30). Comparison of findings in patients with GPA with renal involvement in this study with those in other studies is shown in Table 4.

Table 3. Factors related to mortality in patients with GPA according to univariate and multivariate analyses

	Univariate analysis			Multivariate analysis		
Factor	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age ≥65 years*	13.4	1.3-135.4	0.028	0.147	0.023-0.960	0.045
Smokers	5.4	0.8-36.7	0.088			
Renal involvement	0.4	0.02-6.2	0.498			
ENT involvement	0.7	0.1-5.7	0.744			
SCr ≥1.4*	30.9	1.2-787.7	0.038	0.213	0.051-0.883	0.033
Htc <30%*	1.6	0.2-16.5	0.688			
Proteinuria ≥500 mg/day*	2.1	0.3-17.1	0.487			
ANCA positivity*	0.2	0.01-3.9	0.282			
Need for RRT	0.157	0.01-2.2	0.166			

*Data obtained at diagnosis
GPA: granulomatosis with polyangiitis; ENT: ear-nose-throat; SCr: serum creatinine; Htc: hematocrit; ANCA: antineutrophil cytoplasm antibody; RRT: renal replacement therapy; OR: odds ratio; CI: confidence interval

Table 4. Comparison of findings in patients with GPA with renal involvement in this study with other studies

Characteristics	**Rathi et al. (5) (n=35)**	**Caravaca-Fontán et al. (30) (n=25)**	**Patients with GPA patients with renal involvement in this study (n=33)**
Age at diagnosis, years (mean±SD or median [IQR])	42.7±15.2	58 (15)	50 (32-62.5)
M:F	1.3:1	1.7:1	1.5:1
SCr at presentation (mg/dL) (mean±SD or median [IQR])	3.5±3	6.2 (3.5)	1.69 (0.9-5.6)
Positive ANCA, %	91.4	100	90.9
Renal outcome, chronic RRT, %	2.9	NA	35.5*
Mortality, %	22.9	NA	35.5*
Patient survival (months) (mean±SD or median [IQR])	35.3±12.5	NA	39 (17-87)

*2 patients were lost to follow-up
GPA: granulomatosis with polyangiitis; M: male; F: female; SCr: serum creatinine; IQR: interquartile range; SD: standard deviation; ANCA: antineutrophil cytoplasm antibody; RRT: renal replacement therapy; NA: not available

Although SCr level at presentation in our series was lower than in the series reported by Rathi et al. (5), chronic RRT rates were higher in our series. It could be owing to the biopsy rates; 25 patients with AAV (49%) reported by Rathi et al. (5) versus 24.2% of patients in our series. In addition, the patients in our series were relatively older than the patients reported by Rathi et al. (5).

An interesting finding of our study was that ENT involvement was shown to be more common in patients with GPA without renal involvement than in patients with renal involvement. This finding was observed in all the patients with AAV by Rathi et al. (70.7% vs. 49%, p=0.036) (5).

In our cohort, 20.8% of the patients developed ESRD at the end of the follow-up (median, 51 months). Holle et al. (29) showed that dialysis-dependent ESRD rate dropped from 10.3% in their earliest cohort (1966-1993 to 1997) to 4.1% in their second (1994-1998 to 2005) and to 1.2% in their third cohort (1999-2002 to 2005). Orden et al. (21) found the frequency of dialysis as 10.8% among their patients with severe GPA. Koldingsnes et al. (9) found ESRD in 10 (17.9%) patients, and renal survival rates for 1, 5, and 10 years were 93%, 86%, and 77%, respectively after 4.5 years.

The overall mortality rate in our cohort was 28.3%, comparable to that observed in the largest series of patients with GPA in other countries. Despite current treatment modalities, the patients with GPA have a higher mortality risk especially in the first year of their disease owing to infection, active vasculitis, and renal failure (2, 24, 25). In our study, 73.3% of the deaths

Table 5. Comparison of clinical features and outcomes of patients with GPA in this study with that of patients in other cohorts published after 2010

Authors/ Country/Number of patients/Years data obtained	de Souza et al. (Brazilian) (n=134) 1999-2009	Sugiyama et al. (Japan) (n=241) 2006-2008	Orden et al. (Argentina) (n=37) 1994-2011	Catanoso et al. (Italy) (n=18) 1995-2009	Wallace et al. (UK) (n=465) 1992-2013	Faurschaou et al. (Denmark) (n=308) 1994-2010	Solans-Laque et al. (Spain) (n=184) 1990-2014	Sharma et al. (India) (n=105) 2005-2016	Wójcik et al. (Poland) (n=417) 1990-2016	Turkey (n=53) 2000-2014
Publication year/ reference no	2010/25	2013/22	2013/21	2014/24	2015/2	2015/23	2017/20	2017/26	2019/33	
Age at diagnosis, years (mean±SD or median [IQR])	43.4±15.5	58.4±1.1	48.5±12	58.8±20.2	60.3±14.6	56 (70)	49.9±16.3	40 (23.5)	51.4 (67)	47.1±16.3
Men, %	47.8	58	51.3	61	52.7	49.3	51.1	42.9	50.4	60.4
SCr at presentation (mg/dL)	2.7 (3.3)	1.6±0.2	NA	NA	NA	NA	1.7±1.9	NA	NA	1 (2.2)
Positive ANCA, n (%)										
c-ANCA, n (%)	61.9	73	86.5	78.6	NA	NA	73.9	81.9	85.6	81.1
p-ANCA, n (%)	12.9	17.4	5.4	21.4	NA	NA	14.7	6.7	4.7	15.1
Lung involvement	77.6	78	81.1	55.6	NA	NA	62.5	67.6	75.5	73.6
Renal involvement	75.4	60.6	81.1	55.6	NA	NA	56	51.4	60.4	63.5
ENT involvement	85.8	86.7	48.6	55.6	NA	NA	72.3	79	75.5	62.3
Ophthalmic involvement	35.8	46.1	27.0	NA	NA	NA	23.9	40.9	27.3	28.3
Need for permanent RRT, n (%)*	19.4	NA	10.8	NA	NA	NA	NA	NA	13.2	20.8
Mortality, n (%)*	21.6	NA	37.8	27.7	21.7	25.9	22.3	17.4	10.1	28.3
Patient survival, months (median [IQR])*	NA	NA	NA	22 (NA)	NA	NA	73 (135)	NA	NA	51 (89.5)

*3 patients were lost to follow-up
GPA: granulomatosis with polyangiitis; c-ANCA: cytoplasmic antineutrophil cytoplasm antibody; ENT: ear-nose-throat; p-ANCA: perinuclear antineutrophil cytoplasm antibody; SCr: serum creatinine; IQR: interquartile range; RRT: renal replacement therapy; NA: not available; SD: standard deviation

occurred during the first year. Increased mortality has been reported as an association with older age (>50 years) (7, 9, 10, 24), kidney involvement (with impaired renal function) (7-10, 28, 31, 32), and pulmonary manifestations at diagnosis (7). In contrast, Wallace et al. (2) did not find any significant difference between patients older and younger than 65 years of age and between male and female patients. Koldingsnes and Nossent (9) found that increased age, dialysis dependence, and organ damage at baseline were the most important predictors of reduced patient survival. The Polish vasculitis registry also found death-related factors as age at diagnosis over 65 years, chronic RRT, and lower respiratory tract involvement in patients with GPA (33). Patient survival in our study tended to be lower than that in previous studies, which reported a survival between 85% and 97% at 1 year, 69% and 91% at 5 years, and 68% and 88% at 10 years (9, 12, 21, 24, 34, 35). We found that clinical variables with the greatest impact in mortality were SCr level at diagnosis ≥1.4 mg/dL and age at diagnosis ≥65 years. The clinical features and outcomes of our patients and those of European and American cohorts published after 2010 are compared and reviewed in Table 5.

This study has limitations. First, casual relationships could not be established because this was a retrospective study. Second, the study was conducted in a single center; therefore, the number of patients was relatively small. Third, the medical records were reevaluated, and all the patients, except 3 of them, were contacted by telephone to confirm the prognosis. We could not obtain reliable data on the causes of death in 7 of our patients.

CONCLUSION

The prognosis of GPA is associated with high mortality or development of end-stage renal failure. The survival of patients with GPA is closely associated with age and renal function at admission. We believe that the delay in diagnosis could have influenced the development of irreversible kidney damage, which in turn was one of the significant mortality determinants. Therefore, early referral to nephrology from other departments is important. Larger series and prospective studies are needed to show the impact of renal involvement and early referral to nephrologists on the prognosis of patients with GPA.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Cerrahpaşa School of Medicine, İstanbul University-Cerrahpaşa (Approval Date: September 04, 2012; Approval Number: 26694).

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