10.5152/turkjnephrol.2022.21026

**Original Article**

Turkish Journal of Nephrology

# Clinicopathological Features and Kidney Survival in Rapidly Progressive Glomerulonephritis: A Single-Center Experience

Mehmet Akif Eksin[1], Ebru Gök Oğuz[2], Kadir Gökhan Atılgan[2], Hatice Şahin[2], Tamer Selen[2], Gülay Ulusal Okyay[2], Fatma Ayerden Ebinç[2], Mehmet Deniz Aylı[2]

[1]Department of Internal Medicine, University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey
[2]Department of Nephrology, University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey



## ABSTRACT

**Objective:** Advanced age, need for dialysis and high creatinine values at the time of admission, anti-glomerular basement membrane antibody positivity, pulmonary hemorrhage, and fibrous crescents on pathology are known poor prognostic factors in rapidly progressive glomerulonephritis. Our study aimed to determine the clinical, laboratory, and pathological factors affecting the kidney prognosis in the progression to end-stage kidney failure disease in our rapidly progressive glomerulonephritis patients.
**Methods:** This study was made with 52 patients diagnosed with type 1 and type 3 rapidly progressive glomerulonephritis. The study continued with 37 eligible patients.
**Results:** The patients' mean age was 52.3 ± 11.06 and 22 (59.4%) were male. In 6 patients (16.2%), anti-glomerular basement membrane positivity, in 11 patients (29.7%), cytoplasmic anti-neutrophilic cytoplasmic antibody positivity, and in 20 patients (54.1%), perinuclear anti-neutrophilic cytoplasmic antibody positivity was detected. Parathyroid hormone value was higher in the perinuclear anti-neutrophilic cytoplasmic antibody-positive group at the time of biopsy ($P = .005$). Serum sodium levels were lower at the biopsy time in the patient group with a crescent rate above 65% ($P = .014$). Patients with end-stage kidney failure disease were younger, and their serum sodium levels expressively were lower at the biopsy time ($P = .006$, $P = .02$ respectively). When the risk factors affecting end-stage kidney failure disease were examined in multivariate regression analysis, it was observed that while sodium and parathyroid hormone values were not risk factors at the time of biopsy, age ($P = .048$) and time until diagnosis were risk factors ($P = .048$).
**Conclusion:** In our study, the risk factors affecting end-stage kidney failure disease progression in rapidly progressive glomerulonephritis patients were age and the time until diagnosis. Kidney biopsy is essential for the kidney prognosis for rapid diagnosis, especially in young patients with suspected rapidly progressive glomerulonephritis.
**Keywords:** Renal survival, rapidly progressive glomerulonephritis, anti-ANCA, anti-GBM

**Corresponding author:** Ebru Gök Oğuz ✉ ebrugokoguz@hotmail.com
**Received:** January 14, 2021 **Accepted:** August 9, 2021

**Cite this article as:** Eksin MA, Gök Oğuz E, Atılgan KG, et al. Clinicopathological features and kidney survival in rapidly progressive glomerulonephritis: A single-center experience. *Turk J Nephrol.* 2022;31(2):138-147.

## INTRODUCTION

Rapidly progressive glomerulonephritis (RPGN) is a rare, life-threatening condition that causes progressive kidney function loss within days, weeks, or months due to severe glomerular damage.[1]

Clinically, it is a picture in which loss of kidney functions are observed together with acute nephritic syndrome features such as microscopic or macroscopic hematuria, erythrocyte casts in the urine, and proteinuria. Regardless of the cause, the classical histopathological lesion accompanying the clinical syndrome is excessive extracapillary proliferation, called crescent formation, affecting more than 50% of the glomeruli. The classification of crescentic glomerulonephritis can be grouped under 3 main headings: anti-glomerular basement antibody (anti-GBM) disease (type 1), immune complexes mediated type (type 2), little or no immune deposits "pauci immune" type (type 3).[2] If treatment is not started early, cellular crescents rapidly transform into

This work is licensed under a Creative Commons Attribution 4.0 International License.

fibrous crescents and collapse occurs in the glomerular capillary system.[3,4]

Although RPGN is rapidly treated in nephrology, it is a group of diseases that can have a poor prognosis according to their types. The known poor prognostic factors are elderly patients, dialysis need at the time of admission, high creatinine value, anti-GBM antibody positivity, pulmonary hemorrhage, and fibrous crescents in pathology.[5,6]

In this study, we evaluated 37 patients diagnosed with type 1 and type 3 RPGN with at least 1-year follow-up results. Our study aimed to determine the clinical, laboratory, and pathological risk factors affecting the renal prognosis in our RPGN patients with crescentic glomerulonephritis who were followed up in our clinic.

## METHODS

In the study, the files of 52 patients diagnosed with type 1 and type 3 RPGN by kidney biopsy between 2012 and 2018 in the Nephrology Clinic of Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital were retrospectively analyzed. Patients between the ages of 18-70 and followed up for at least 1 year were included as inclusion criteria. In our study, exclusion criteria were those without active outpatient follow-up, serologically negative type 3 RPGN, and type 2 RPGN patients. Since the number of serologically negative type 3 RPGN and type 2 RPGN patients with follow-up was low, they were not included in our study. The study continued with 37 eligible patients. All patients were included in the study after signing informed consent forms. The study was performed under the Declaration of Helsinki. The study design was approved by the local ethical committee (date: November 12, 2018; reference number: 56/19).

### Treatment Protocol

All patients were treated with standard immunosuppressive treatment protocols by the Kidney Disease: Improving Global Outcomes 2012 glomerulonephritis guideline and the European Vasculitis Society (EUVAS) by evaluating current laboratory results with clinical, physical examination, and pathology findings.[7,8] Pulse steroids (maximum cumulative dose 1-3 g) were given to all cases for 3 days. The steroid dose was reduced to 5 mg at 6 months in maintenance therapy. Steroid dosage in the next period varied according to guidelines and physicians who followed. In addition to steroids, cyclophosphamide (0.75 g/m$^2$ intravenously) was given every 3-4 weeks, the dose was decreased to 0.5 g/m$^2$ if the age was >60 years or GFR was <20 mL/min per 1.73 m$^2$. In this study, plasmapheresis was performed on an average of 7-10 times at a dose of 60 mL/kg/session. The replacement fluid was given to the patients as fresh frozen plasma, considering bleeding risk.

Pulmonary involvement is determined by clinical and radiological evaluation; severe pulmonary involvement was considered as cases with severe hemoptysis and oxygen saturation below 85% under oxygen therapy.

Assessment of disease activity was performed using the Birmingham Vasculitis Activity Scoring (BVAS), a comprehensive scoring system that includes a 9-part organ and system query. Clinical remission as per the European League Against Rheumatism/EUVAS is stated to be 0 for the BVAS.[8] After 3 doses of cyclophosphamide were given in the treatment, cyclophosphamide was completed to 6 doses depending on whether the patient was dialysis-dependent or not and extrarenal findings. Cyclophosphamide was given once a month until remission was achieved in 6-12 courses. In our study, we did not have any patients receiving rituximab. Maintenance treatment was based on azathioprine combined with low-dose corticosteroid (CS).

### c-ANCA, p-ANCA and Anti - GBM Measurement

The enzyme-linked immunosorbent assay and immunofluorescence assay methods were used to measure the cytoplasmic anti-neutrophilic cytoplasmic antibody (c-ANCA), perinuclear anti-neutrophilic cytoplasmic antibody (p-ANCA), and anti-GBM values of the patients in this study.

### Statistical Analysis

In statistical analysis, categorical variables were given as numbers and percentages. Descriptive statistics mean ± standard deviation and median (min-max value) were used depending on the variables' normal distribution state. Normal distribution was evaluated with Kolmogorov–Smirnov/Shapiro–Wilk tests. Chi-square tests were used for the comparison of categorical variables between groups. Student's *t*-test or Mann–Whitney *U* test was used for the comparison of data sets. The receiver operating characteristic curve analysis was used to calculate the threshold values for serum creatinine levels and the number of crescentic glomeruli.

Binary logistic regression analysis was used to determine the end-stage kidney failure disease (ESKD) state's independent

### MAIN POINTS

- The classification of crescentic glomerulonephritis can be grouped under 3 main headings: anti-glomerular basement antibody (anti-GBM) disease (type 1), immune complexes mediated type (type 2), little or no immune deposits"pauci immune" type (type 3).
- Advanced age, need for dialysis and high creatinine values at the time of admission, anti-glomerular basement membrane antibody positivity, pulmonary hemorrhage, and fibrous crescents on pathology are known poor prognostic factors in rapidly progressive glomerulonephritis.
- Plasmapheresis should be added to the treatment of RPGN patients with severe renal insufficiency (need for dialysis or rapid creatinine increase), pulmonary hemorrhage due to vasculitis or ANCA and anti-GBM positivity.

risk factors. Clinically relevant variables and/or variables with $P < .05$ as determined in univariate analyses were entered into binary logistic regression analysis after excluding multicollinear variables. The odds ratios with corresponding 95% CIs were used to show the factors affecting the outcomes. $P < .05$ was accepted to be statistically significant. SPSS software 22.0 (IBM Corp., Armonk, NY, USA) was used for analysis.

## RESULTS

In the study, 37 patients diagnosed with type 1 and type 3 RPGN were included. The patients' mean age was 52.3 ± 11.06 years and 22 (59.4%) were male. The mean follow-up time of the patients was 32.6 ± 12.8 months. When the serological evaluation was performed, anti-GBM positivity was detected in 6 (16.2%) of our patients, c-ANCA positivity in 11 (29.7%), and p-ANCA positivity in 20 (54.1%) of our patients. When we divided the patients into 3 groups according to antibody positivity by looking at their serology and when the demographic, clinical, and pathological data were evaluated (Table 1), anti-GBM was more common in women (66.7%), c- ANCA was more common in men (90.9%), and p-ANCA was seen equally in 2 genders ($P$ = .031). In the anti-GBM positive group, the rate of hemoptysis was the highest (66.7%), the time from the moment of admission to the hospital to diagnosis was the longest (17 ± 0.6 days), and the development of ESKD was the most frequent (100%) ($P$ = .022, $P$ = .001, $P < .001$, respectively). It was observed that the rate of dialysis requirement at the time of diagnosis was statistically significantly higher in the anti -GBM and c-ANCA-positive group compared to the p-ANCA-positive group ($P$ = .018). The BVAS score used for disease activation was determined as 6.2 ± 2.2 at the time of biopsy. When the laboratory findings at the time of biopsy were evaluated among the patient groups, it was observed that the parathyroid hormone (PTH) value was higher in the p-ANCA-positive patient group ($P$ = .005). Kidney biopsy findings of the patients are shown in Table 1 and there was no difference between the 3 groups in terms of kidney biopsy findings ($P > .05$).

The rate of applying plasmapheresis treatment was statistically significantly higher in the anti-GBM and c-ANCA-positive groups than in the p-ANCA-positive group ($P$ = .013). In our study, 6 of 25 patients who did not develop ESKD were in remission (Table 1, n = 2 c-ANCA, n = 4 p-ANCA).

Through the receiver operating characteristic curve analysis, the threshold value of serum creatinine level at admission was found to be 6 mg/dL with 75% sensitivity and 68% specificity. Seventeen patients had a creatinine value higher than 6 mg/dL, and 20 patients had a creatinine value lower than 6 mg/dL (Table 2). It was observed that the rate of hemoptysis was higher in the patient group with serum creatinine value higher than 6 mg/dL, the meantime from the moment of admission to the hospital to diagnosis was longer, and the rate of dialysis needed at the time of diagnosis was higher ($P$ = .001, $P$ = .039, and $P < .001$, respectively). It was observed that the rate of the average crescent, plasmapheresis treatment, and ESKD development was more frequent in the patient group with serum creatinine levels higher than 6 mg/dL ($P$ = .003, $P < .001$, and $P$ = .014, respectively). The p-ANCA positivity frequency was statistically significantly lower in the group with serum creatinine value higher than 6 mg/dL ($P$ = .006).

Using the receiver operating characteristic curve analysis, the average crescent rate's threshold value was 65% with 75% sensitivity and 52% specificity. While the number of patients with a crescent rate above 65% was 21, the number of patients below 65% was 16 (Table 2). It was found that the rate of hemoptysis was higher, and the rate of dialysis requirement at the time of diagnosis was more frequent in the patient group with a crescent rate above 65% ($P$ = .018 and $P$ = .018, respectively). It was found that the serum creatinine levels were higher, and the serum sodium levels were lower in the patient group with a crescent rate above 65% ($P$ = .019 and $P$ = .014, respectively). The frequency of p-ANCA positivity was statistically significantly lower in the group with a crescent ratio of over 65% ($P$ = .004).

In our study, the mean follow-up period was 32.6 ± 12.8 months (Table 1). It was evaluated that 12 of our patients developed ESKD and 25 were followed up with treatment. Of the 12 patients, 6 were anti-GBM positive, 3 were c-ANCA positive, and 3 were p-ANCA positive. At the first year, 10 patients were diagnosed with ESKD (n = 6 anti-GBM, n = 2 c-ANCA, n = 2 p-ANCA), the 1-year kidney survival of the patients was 70.3%. In our study, 5 patients (n = 3 anti-GBM, n = 1 c-ANCA, n = 1 p-ANCA) died during the follow-up and 3 anti-GBM patients died in the first year. Accordingly, 1-year patient survival in our study was 91.8%.

When our patients were evaluated as 2 separate groups with and without ESKD (Table 3), it was found that patients who developed ESKD were younger, the time from admission to diagnosis was longer, and the rate of dialysis need at the time of diagnosis was higher ($P$ = .006, $P$ = .001, and $P$ = .011, respectively). It was observed that the mean hemoglobin and serum sodium levels were lower ($P$ = .016 and $P$ = .02, respectively) and the mean creatinine values were higher in the patient group with ESKD ($P$ = .05). In the group with ESKD, p-ANCA positivity frequency was lower, while anti-GBM positivity frequency was higher ($P$ = .026 and $P < .001$, respectively).

As indicated in Table 4, age, time until diagnosis, need for dialysis at diagnosis, creatinine level at the time of biopsy, sodium level, and p-ANCA were found to be effective in the evaluation of risk factors affecting ESKD ($P$ = .013, $P$ = .005, $P$ = .018, $P$ = .019, $P$ = .033, and $P$ = .019). However, as indicated in Table 5, among these risk factors affecting ESKD, only age and time until

**Table 1.** Clinical and Pathological Evaluation of Patients with Type 1 and Type 3 RPGN

| | All Patients | Anti-GBM | c-ANCA | p-ANCA | *P* |
|---|---|---|---|---|---|
| Demographical data | | | | | |
| Number of patients, n (%) | 37 | 6 | 11 | 20 | |
| Mean age (year) | 52.3 ± 11.06 | 49 ± 7.3 | 50 ± 13.4 | 58 ± 12.5 | .139 |
| Gender | | | | | .031 |
| Male, n (%) | 22 (59.4) | 2 (33.3) | 10 (90.9) | 10 (50) | |
| Female, n (%) | 15 (40.6) | 4 (66.7) | 1 (9.1) | 10 (50) | |
| Mean follow-up time (month) | 32.6 ± 12.8 | 28.3 ± 8.9 | 36.8 ± 12.5 | 31.7 ± 13.9 | .392 |
| Clinical data | | | | | |
| HT, n (%) | 26 (70.2) | 3 (50) | 6 (54.5) | 17 (85) | .102 |
| Hemoptysis, n (%) | 15 ( 40.5) | 4 (66.7) | 7 (63.6) | 4 (20) | .022 |
| Oliguria, n (%) | 37 (100) | 6 (100) | 11 (100) | 20 (100) | - |
| Time until diagnosis[a] (day) | 13.6 ± 2.7 | 17 ± 0.6 | 13 ± 2.8 | 13 ± 2.3 | .001 |
| Dialysis need at the time of diagnosis, n (%) | 22 (59.4) | 6 (100) | 8 (72.7) | 8 (40) | .018 |
| BVAS score | 6.2 ± 2.2 | - | 6.6 ± 2.6 | 6.1 ± 2.0 | .535 |
| Laboratory results | | | | | |
| Hemoglobin (g/dL) | 9.0 ± 1.4 | 8.7 ± 1.7 | 9.1 ± 1.4 | 9.2 ± 1.6 | .800 |
| White Blood Cell ($10^3$/µL) | 10.9 ± 4.3 | 9.2 ± 4.3 | 13.9 ± 4.7 | 9.7 ± 3.3 | .052 |
| Urea (mg/dL) | 152.9 ± 61.8 | 155 ± 76.6 | 169 ± 47.3 | 143 ± 65.3 | .535 |
| Creatinine (mg/dL) | 5.5 ± 3.3 | 8.04 ± 5.29 | 6.15 ± 3.34 | 4.55 ± 2.31 | .067 |
| Sodium (mEq/L) | 136 ± 4.7 | 133 ± 4.5 | 135 ± 5.2 | 137 ± 4.3 | .131 |
| Potassium (mEq/L) | 4.7 ± 0.9 | 4.8 ± 1.4 | 4.6 ± 0.6 | 4.8 ± 1.0 | .763 |
| Calcium (mg/dL) | 8.2 ± 1.0 | 8.1 ± 0,5 | 8.1 ± 0.5 | 8.3 ± 1.4 | .887 |
| Phosphorus (mg/dL) | 5.1 ± 1.5 | 5.1 ± 1.9 | 5.2 ± 1.6 | 5.2 ± 1.6 | .992 |
| Uric acid (mg/dL) | 8.4 ± 2.3 | 8.2 ± 2.4 | 9.3 ± 2.7 | 8.0 ± 2.1 | .342 |
| 25-(OH) $D_3$ levels (ng/mL) | 11.7 ± 10.3 | 12.1 ± 8.1 | 12.9 ± 15.8 | 10.9 ± 7.3 | .807 |
| PTH[b] (pg/mL), median (min-max) | 120 (28-429) | 49 (40-86) | 82 (28-142) | 150 (35-429) | .005 |
| Serum protein (g/dL) | 6.2 ± 0.9 | 6.3 ± 0.9 | 6.2 ± 0.9 | 6.3 ± 1.1 | .975 |
| Albumin (g/dL) | 2.9 ± 0.6 | 3.1 ± 0.7 | 2.7 ± 0.8 | 3.1 ± 0.5 | .299 |
| eGFR (mL/min/1.73 $m^2$) CKD-EPI | 16.3 ± 15.5 | 14.6 ± 22.2 | 15.5 ± 12.6 | 17.4 ± 15.4 | .191 |
| Proteinuria (g/day) | 3.2 ± 5.1 | 2.6 ± 1.3 | 5.5 ± 9.0 | 2.1 ± 1.5 | .278 |
| Sedimentation rate (mm/h), median (min-max) | 50 (11-883) | 47 (38-67) | 69 (12-120) | 49 (11-883) | .708 |
| CRP (mg/dL), median (min-max) | 62.2 (3-461) | 60 (3-461) | 108 (8-232) | 52 (3-145) | .346 |
| Kidney biopsy findings | | | | | |
| Mean glomerulus number | 16.6 ± 2.7 | 17.6 ± 3.5 | 16.9 ± 2.8 | 16.2 ± 2.4 | .491 |
| Crescentic glomeruli ratio (%) | 67.9 ± 13.3 | 80 ± 15.9 | 75 ± 15.2 | 63 ± 12.0 | .052 |
| Fibrocellular crescentic glomeruli ratio (%)[c] | 30.4 ± 13.0 | 50.8 ± 6.6 | 28.1 ± 11.0 | 25.5 ± 9.4 | <.001 |
| Cellular crescentic glomeruli ratio (%)[d] | 37.5 ± 11.2 | 29.1 ± 10.6 | 43.6 ± 13.4 | 36.7 ± 8.3 | .030 |
| Glomerulosclerosis ratio (%) | 21.6 ± 19.7 | 19.3 ± 19.5 | 13.5 ± 11.6 | 26.9 ± 22.4 | .296 |

(*Continued*)

| | All Patients | Anti-GBM | c-ANCA | p-ANCA | *P* |
|---|---|---|---|---|---|
| Treatment | | | | | |
| Plasmapheresis treatment, n (%) | 26 (70.2) | 6 (100) | 10 (90.9) | 10 (50) | .013 |
| Clinical outcomes | | | | | |
| Remission, n (%) | 6 (16.21) | 0 | 2 (18.2) | 4 (20.0) | .496 |
| ESKD, n (%) | 12 (100) | 6 (100) | 3 (27.3) | 3 (15.0) | <.001 |

[a]Time until diagnosis; GBM versus c-ANCA, *P* = .003; GBM versus p-ANCA, *P* = .001.
[b]PTH; p-ANCA versus GBM, .009; p-ANCA versus c-ANCA, *P* = .014.
[c]Fibrocellular crescentic glomeruli ratio; GBM versus p-ANCA, *P* < .001; GBM versus c-ANCA, *P* < .001.
[d]Cellular crescentic glomeruli ratio, c-ANCA versus GBM, *P* = .029.
RPGN, rapidly progressive glomerulonephritis; GBM, glomerular basement membrane; c-ANCA, cytoplasmic anti-neutrophilic cytoplasmic antibody; p-ANCA, perinuclear anti-neutrophilic cytoplasmic antibody; HT, hypertension; BVAS, Birmingham vasculitis activity score; PTH, parathyroid hormone; eGFR, estimation glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRP, C-reactive protein; ESKD, end-stage kidney disease.

diagnosis were found to be effective in multivariate regression analysis (*P* = .048 and *P* = .048).



## DISCUSSION

In this study, consistent with the literature, in our 37 patients who were followed up for 1 year with a diagnosis of type 1 and type 3 RPGN, the most common etiological serological reason was ANCA positivity. However, p-ANCA positivity was higher than c-ANCA positivity (Table 1).[9] Anti-GBM positivity was more common in females, c-ANCA positivity was more common in males, while p-ANCA positivity was found equally in both genders (Table 1). When we look at the literature, we see that anti-GBM and p-ANCA positivity is slightly higher in males and c-ANCA positivity is equal in both genders.[10]

Hemoptysis and the need for dialysis at the time of diagnosis are very important in the initial treatment selection in RPGN.[11,12] In this study, hemoptysis and the need for dialysis at the time of diagnosis were recorded more frequently in those with anti-GBM- and c-ANCA-positive patients. Plasmapheresis should be added to the treatment of RPGN patients with severe kidney insufficiency (need for dialysis or rapid creatinine increase), pulmonary hemorrhage due to vasculitis or ANCA and anti-GBM positivity.[7,13,14] In our study, 26 patients received plasmapheresis treatment. The need for plasmapheresis treatment was higher in the patient group with anti-GBM-positive and c-ANCA-positive patients in this study. In recent studies, the effect of plasmapheresis on patient survival in ANCA-associated vasculitis (AAV) has been questioned. The Plasma Exchange and Glucocorticoid Dosing in the Treatment of Anti-Neutrophil Cytoplasm Antibody Associated Vasculitis study investigating the appropriate treatment options for ANCA-associated vasculitis (AAV) is the largest scale, multicenter, and randomized controlled study in the literature. Walsh et al[15] investigated the effects of plasmapheresis primarily on the patient outcomes in the cases with severe AAV (severe definition: GFR <50 mL/min or diffuse pulmonary hemorrhage). The primary outcomes of this study were determined as all-cause mortality or ESKD. As a result, it has been shown that plasmapheresis, in addition to standard treatment, does not provide additional benefit for severe AAV.[15]

When we look at the time from the moment of presentation to the diagnosis of the disease, it was seen that this period was longer in the patient group with anti-GBM positivity. Among the reasons for the delay in diagnosis, it can be said that kidney biopsy was delayed due to the poor general condition of the patients. Serological tests (anti-GBM) may have caused delayed kidney biopsy in these patients due to the late results in our clinic. Kidney and patient survival times are poor in anti-GBM disease and aggressive treatment should be given with rapid diagnosis.[16,17] Patients with serum creatinine <5.7 mg/dL (<504 µmol/L) at baseline had 100% 1-year patient survival, 95% kidney survival, and 94% both patient and kidney survival at 5 years. In patients with baseline serum creatinine >5.7 mg/dL (>504 µmol/L) and not requiring urgent dialysis, patient and kidney survival were 83% and 82% at 1 year, 80%, and 50% at 5 years, respectively. However, in patients who needed dialysis initially, patient and kidney survival decreased to 65% and 8% in the first year, and 44% and 13% in the fifth year, respectively.[18] In this study, the risk of developing ESRD was higher in the anti-GBM-positive patient group. In our study, 12 patients developed ESKD, and all 6 patients with anti-GBM-positive progressed to ESKD during follow-up.

Parathyroid hormone elevation at the kidney biopsy time was significantly higher in the patient group with p-ANCA positivity (Table 1) in this study. There is no information on this subject in the literature to date. The fact that there is no difference between the 25(OH)$D_3$ level, and calcium and phosphorus levels between the groups suggests that the higher PTH in the p-ANCA positive group may be due to pathogenesis different from calcium–phosphorus metabolism. In our study, as seen in Table 1, the rate of glomerulosclerosis was higher in the p-ANCA group compared to the other 2 groups, although it was not significant. This finding suggests that the cause of high PTH in the p-ANCA group may be due to chronic cases that take a long time to diagnose.

**Table 2.** Comparison of Patients According to Serum Creatinine Values and Crescentic Glomerule Ratios at the Time of Admission

| | Serum Creatinine | | | Crescent Ratio | | |
|---|---|---|---|---|---|---|
| | ≤6.0 mg/dL | >6 mg/dL | *P* | ≤65 | >65 | *P* |
| Demographical data | | | | | | |
| Number of patients, n (%) | 20 | 17 | | 16 | 21 | |
| Mean age (year) | 56 ± 13.9 | 52 ± 10.9 | .333 | 58 ± 11.8 | 51 ± 12.5 | .075 |
| Gender | | | .052 | | | .306 |
| Male, n (%) | 9 (45.0) | 13 (76.5) | | 8 (50.0) | 14 (66.7) | |
| Female, n (%) | 11 (55.0) | 4 (23.5) | | 8 (50.0) | 7 (33.3) | |
| Clinical data | | | | | | |
| HT, n (%) | 15 (75) | 11 (64.7) | .495 | 14 (87.5) | 12 (57.1) | .495 |
| Hemoptysis, n (%) | 3 (15) | 12 (70.6) | .001 | 3 (18.8) | 12 (57.1) | .018 |
| Oliguria, n (%) | 20 (100) | 17 (100) | - | 16 (100) | 21 (100) | - |
| Time until diagnosis (day) | 13 ± 2.4 | 15 ± 2.8 | .039 | 13 ± 2.3 | 13 ± 2.9 | .135 |
| Dialysis need at the time of diagnosis (%) | 6 (30) | 16 (94.1) | <.001 | 6 (37.5) | 16 (76.2) | .018 |
| Laboratory results | | | | | | |
| Hemoglobin (g/dL) | 9.1 ± 1.6 | 9.1 ± 1.4 | .928 | 9.3 ± 1.5 | 8.9 ± 1.5 | .443 |
| White blood cell ($10^3$/µL) | 10.4 ± 4.1 | 11.4 ± 4.7 | .471 | 11.0 ± 3.7 | 10.7 ± 4.8 | .861 |
| Urea (mg/dL) | 121 ± 61.2 | 191 ± 36.5 | .001 | 132 ± 60.6 | 169 ± 59.3 | .07 |
| Creatinine (mg/dL) | | | | 4.1 ± 2.25 | 6.7 ± 3.72 | .019 |
| Sodium (mEq/L) | 137 ± 3.6 | 134 ± 5.5 | .066 | 138 ± 3.4 | 134 ± 5.0 | .014 |
| Potassium (mEq/L) | 4.7 ± 0.8 | 4.8 ± 1.1 | .880 | 4.8 ± 0.8 | 4.7 ± 1.0 | .663 |
| Calcium (mg/dL) | 8.3 ± 1.3 | 8.1 ± 0.6 | .582 | 8.4 ± 1.4 | 8.1 ± 0.7 | .416 |
| PhosphorS (mg/dL) | 5.1 ± 1.5 | 5.3 ± 1.7 | .637 | 4.8 ± 1.5 | 5.4 ± 1.7 | .294 |
| Uric acid (mg/dL) | 8.1 ± 1.8 | 8.9 ± 2.8 | .258 | 7.9 ± 1.7 | 8.9 ± 2.7 | .220 |
| 25-(OH) $D_3$ levels (ng/mL) | 13.5±12.9 | 9,6±5,6 | .594 | 14.5±13.2 | 9.6±7.1 | .182 |
| PTH (pg/mL) | 126 (28-429) | 86 (35-331) | .497 | 124 (28-429) | 101 (40-331) | .916 |
| Total protein (g/dL) | 6.3 ± 0.9 | 6.3 ± 0.9 | .915 | 6.5 ± 1.0 | 6.1 ± 0.9 | .188 |
| Albumin (g/dL) | 3.1 ± 0.6 | 2.9 ± 0.7 | .502 | 3.2 ± 0.6 | 2.8 ± 0.7 | .062 |
| eGFR (mL/min/1.73 $m^2$), CKD-EPI | 25 ± 17.1 | 7 ± 2.3 | <.001 | 20 ± 17.1 | 13 ± 13.9 | .055 |
| Proteinuria (g/day) | 3.7 ± 6.8 | 2.6 ± 1.8 | 1.00 | 3.9 ± 7.6 | 2.6 ± 1.7 | .592 |
| Sedimentation rate (mm/h) | 59 (21-883) | 49 (11-120) | .311 | 46 (11-104) | 51 (11-883) | .575 |
| CRP (mg/dL) | 61 (3-461) | 65 (3-337) | .729 | 38 (3-120) | 86 (3-461) | .073 |
| c ANCA+ n (%) | 4 (20) | 7 (41.2) | .160 | 2 (12.5) | 9 (42.9) | .071 |
| p ANCA+ n (%) | 15 (75) | 5 (29.4) | .006 | 13 (81.2) | 7 (33.3) | .004 |
| Anti-GBM + n (%) | 1 (5) | 5 (29.4) | .075 | 1 (6.2) | 5 (23.8) | .206 |
| Kidney biopsy findings | | | | | | |
| Mean glomerulus number | 16.0 ± 2.6 | 17.4 ± 2.6 | .118 | 16.1 ± 2.6 | 17.0 ± 2.7 | .377 |
| Crescentic glomeruli ratio (%) | 63 ± 13.1 | 77 ± 13.6 | .003 | 54.7 ± 3.8 | 78.1 ± 7.8 | <.001 |
| Fibrocellular crescentic glomeruli ratio (%) | 24.2 ± 9.9 | 37.6 ± 12.8 | .001 | 23.1 ± 7.2 | 35.9 ± 13.9 | .001 |

(*Continued*)

| | Serum Creatinine | | | Crescent Ratio | | |
|---|---|---|---|---|---|---|
| | ≤6.0 mg/dL | >6 mg/dL | *P* | ≤65 | >65 | *P* |
| Cellular crescentic glomeruli ratio (%) | 37.2 ± 10.9 | 37.9 ± 11.8 | .856 | 31.5 ± 8.5 | 42.1 ± 11.0 | .003 |
| Glomerulosclerosis ratio (%) | 25 ± 20.4 | 18 ± 18.9 | .164 | 27 ± 19.9 | 18 ± 19.2 | .120 |
| Treatment | | | | | | |
| Plasmapheresis treatment, n (%) | 9 (45) | 17 (100) | <.001 | 9 (56.2) | 17 (81) | .151 |
| Clinical outcomes | | | | | | |
| Remission, n (%) | 3 (15) | 3 (17.6) | .587 | 3 (18.8) | 3 (14.3) | .528 |
| ESKD, n (%) | 3 (15) | 9 (52.9) | .014 | 3 (18.8) | 9 (42.9) | .121 |

HT, hypertension; PTH, parathyroid hormone; eGFR, estimation glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRP, C-reactive Protein; c-ANCA, cytoplasmic-anti neutrophilic cytoplasmic antibody; p-ANCA, perinuclear-anti neutrophilic cytoplasmic antibody; GBM, glomerular basement membrane; ESKD, end-stage kidney disease.



In the literature, it has been shown that patients with high initial creatinine value have a poor prognosis and require dialysis. This situation is critical in the initial treatment decision in RPGN patients.[18,19] In Table 2, we grouped our patients according to their serum creatinine value at the time of admission. This grouping was made according to this value since the average serum creatinine value was calculated as 6 mg/dL in our statistical analysis. In line with the literature[18], hemoptysis, need for dialysis at the time of diagnosis, crescent rate, and ESKD development were higher and the time, until diagnosis was longer in the patient group whose initial creatinine value, was higher than 6 mg/dL.

In our study, it was determined that the incidence of hemoptysis was higher in the patient group with a crescent rate above 65%; the initial serum creatinine values and the rate of dialysis requirement in this patient group at the time of diagnosis were found to be consistent with other studies.[20] Differently in this study, we found that the initial serum sodium levels were lower in the patient group with a crescent rate above 65%. Aydın et al[21] in the correlation analysis in their study of RPGN patients found a significant negative correlation between crescent rate and calcium ($P < .001$) and eGFR ($P = .005$). In this study, the reason for lower calcium and sodium levels in patients with more than 65% crescents in kidney biopsy may be due to glomerulosclerosis, namely chronic kidney disease, which is high in this group.

In our study, we divided our patients into 2 groups as ESKD developing and non-developing and analyzed them. Table 3 shows that the patients with ESKD were younger. When we look at the literature data, we see that advanced age is a poor prognostic factor.[22] The main reasons for this are the death of elderly patients due to comorbid conditions until admission to the nephrology service, failure to perform the kidney biopsy in consequence of poor general conditions, difficulty in diagnosis as a result of kidney failure because of drug use, contrast agents and infections, and refusal of kidney biopsy in older people. We thought that the other reason might be that anti-GBM patients were younger than c-ANCA- and p-ANCA-positive patients, although it was not significant as seen in Table 1. Considering from the moment of admission to the hospital to the diagnosis of the disease, we found that this period was longer in the patient group with ESKD. Therefore, correction of the factors that delay the diagnosis is vital.[23] We established that ESKD development incidence was higher in patients who needed dialysis at presentation and had high serum creatinine values. This situation was also one of the risk factors known in the literature.[24,25] We found that the serum sodium levels were low in the group with ESKD (Table 3). We thought that these data are not one of the known risk factors for ESKD development, which may be due to hypervolemia because of kidney failure. In our study age, time until diagnosis, the need for dialysis at the time of diagnosis, creatinine level, sodium level, and p-ANCA at the time of biopsy were found to be risk factors in univariate regression analysis of risk factors that are thought to be risk factors on kidney prognosis (Table 4, $P = .013$, $P = .005$, $P = .018$, $P = .019$, $P = .033$, and $P = .019$). However, when multivariate regression analysis of these risk factors affecting ESKD was performed, it was found that only age ($P = .048$) and time until diagnosis ($P = .048$) were risk factors (Table 5).

In our study, 6 of 25 patients who did not develop ESKD during a mean follow-up period of 32.6 ± 12.8 months were in remission. In various studies, 1-year kidney survival rate in chronic glomerulonephritis (CGN) has been 52%-72%.[26,27] We found that our patients' 1-year kidney survival rate was 70.3% and our patient survival rate was 91.8%. Our results seem to be consistent with the literature.

The most important limitations of the study were that it did not include type 2 RPGN patients, it was retrospective, and the number of our patients was low.

## CONCLUSION

As a result, RPGN is a serious condition in patients with acute kidney failure accompanied by nephritic syndrome findings

**Table 3.** Comparison of Clinical, Laboratory, and Biopsy Findings of Patients With and Without End-Stage Kidney Failure

| | ESKD | | |
|---|---|---|---|
| | **Absent** | **Present** | ***P*** |
| Demographical data | | | |
| Number of patients, n (%) | 25 | 12 | |
| Mean age (year) | 58 ± 11.4 | 46 ± 11.6 | .006 |
| Gender | | | 1.00 |
| Male, n (%) | 15 (60.0) | 7 (58.3) | |
| Female, n (%) | 10 (40.0) | 5 (41.7) | |
| Clinical data | | | |
| HT, n (%) | 18 (72) | 8 (66.7) | 1.00 |
| Hemoptysis, n (%) | 9 (36) | 6 (50) | .488 |
| Oliguria, n (%) | 25 (100) | 12 (100) | - |
| Time until diagnosis (day) | 13 ± 2.3 | 16 ± 2.6 | .001 |
| Dialysis need at the time of diagnosis, n (%) | 11 (44) | 11 (91.7) | .011 |
| Laboratory results | | | |
| Hemoglobin (g/dL) | 9.5 ± 1.3 | 8.2 ± 1.5 | .016 |
| White blood cell (M/L) | 10.9 ± 3.9 | 10.9 ± 5.3 | .941 |
| Urea (mg/dL) | 140 ± 59.1 | 179 ± 61.9 | .074 |
| Creatinine (mg/dL) | 4.8 ± 2.6 | 7.2 ± 4.3 | .050 |
| Sodium (mEq/L) | 137 ± 4.4 | 134 ± 4.6 | .023 |
| Potassium (mEq/L) | 4.6 ± 0.8 | 5.0 ± 1.2 | .263 |
| Calcium (mg/dL) | 8.3 ± 1.2 | 7.9 ± 0.5 | .255 |
| PhosphorS (mg/dL) | 4.9 ± 1.5 | 5.8 ± 1.6 | .088 |
| Uric acid (mg/dL) | 8.4 ± 2.3 | 8.5 ± 2.5 | .879 |
| 25(OH)$D_3$ (ng/mL) | 12.7 ± 11.8 | 9.7 ± 6.4 | .650 |
| PTH (pg/mL) | 127 (28-429) | 53 (35-331) | .025 |
| Total protein (g/dL) | 6.3 ± 0.9 | 6.2 ± 1.03 | .703 |
| Albumin (g/dL) | 3.1 ± 0.6 | 2.8 ± 0.8 | .136 |
| eGFR (mL/min/1.73 $m^2$) CKD-EPI | 17 ± 15.0 | 15 ± 17.2 | .143 |
| Proteinuria (g/day) | 2.2 ± 1.5 | 5.4 ± 8.6 | .140 |
| Sedimentation rate (mm/h) | 51 (12-883) | 47 (11-120) | .661 |
| CRP (mg/dL) | 62 (3-232) | 76 (3-461) | .974 |
| c-ANCA+ n (%) | 8 (32) | 3 (25) | .663 |
| p-ANCA+ n (%) | 17 (68) | 3 (25) | .026 |
| Anti-GBM + n (%) | 0 (0) | 6 (50) | <.001 |
| Kidney biopsy findings | | | |
| Mean glomerulus number | 16.6 ± 2.7 | 16.6 ± 2.7 | .978 |
| Crescentic glomeruli ratio (%) | 67 ± 14.5 | 75 ± 15.1 | .092 |
| Fibrocellular crescentic glomeruli ratio (%) | 22.6 ± 5.4 | 46.6 ± 8.3 | <.001 |
| Cellular crescentic glomeruli ratio (%) | 41.8 ± 9.8 | 28.7 ± 8.5 | <.001 |
| Glomerulosclerosis ratio (%) | 20 ± 19.0 | 25.8 ± 21.2 | .474 |
| Treatment | | | |
| Plasmapheresis treatment, n (%) | 15 (60) | 11 (91.7) | .064 |

HT, hypertension; PTH, parathyroid hormone; GFR, glomerular filtration rate; CRP, C-reactive protein; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; ESKD, end-stage kidney disease; c-ANCA, cytoplasmic anti-neutrophilic cytoplasmic antibody; p-ANCA, perinuclear anti-neutrophilic cytoplasmic antibody; GBM, glomerular basement membrane.

**Table 4.** Univariate Regression Analyses for End-Stage Kidney Failure

| | Univariant Regression | | | |
|---|---|---|---|---|
| | B | OR | 95% CI | *P* |
| Mean age | 0.085 | 1.08 | 1.01-1.16 | .013 |
| Time until diagnosis (day) | −0.498 | 0.61 | 0.43-0.86 | .005 |
| Dialysis need at the time of diagnosis, n (%) | −2.639 | 0.07 | 0.01-0.64 | .018 |
| Creatinine (mg/dL) > 6 mg/dL | 1.852 | 6.37 | 1.34-30.14 | .019 |
| Sodium (mEq/L) | 0.186 | 1.20 | 1.01-1.42 | .033 |
| PTH (pg/mL) | 0.009 | 1.00 | 0.99-1.02 | .113 |
| p-ANCA+ | 1.852 | 6.37 | 1.34-30.14 | .019 |
| Crescentic glomeruli ratio (%) >65% | 1.179 | 3.25 | 0.70-14.92 | .130 |

PTH, parathyroid hormone; p-ANCA, perinuclear anti-neutrophilic cytoplasmic antibody.



**Table 5.** Multivariate Regression Analyses for End-Stage Kidney Failure

| | Multivariate regression | | | |
|---|---|---|---|---|
| | B | OR | 95% CI | *P* |
| Mean age | −0.114 | 0.89 | 0.79-0.99 | .048 |
| Time until diagnosis (day) | 0.490 | 1.63 | 1.00-2.65 | .048 |
| Dialysis need at the time of diagnosis, n (%) | 1.151 | 3.16 | 0.05-208.51 | .590 |
| Creatinine (mg/dL) > 6 mg/dL | 1.480 | 4.39 | 0.24-79.29 | .316 |
| Sodium (mEq/L) | 0.047 | 1.04 | 0.77-1.41 | .757 |
| PTH (pg/mL) | −0.003 | 0.99 | 0.97-1.01 | .749 |
| p-ANCA+ | −0.624 | 1.33 | 0.02-13.22 | .703 |
| Crescentic glomeruli ratio (%) >65% | −0.290 | 0.74 | 0.02-22.72 | .868 |

PTH, parathyroid hormone; p-ANCA, perinuclear anti-neutrophilic cytoplasmic antibody.

and irreversible kidney damage. To minimize morbidity and mortality, it is crucial to perform serological tests and kidney biopsy on suspected patients as early as possible. In this study, the risk factors in ESKD progression in RPGN patients were age and time until diagnosis. Kidney biopsy is essential in kidney prognosis for rapid diagnosis in RPGN suspicion, especially in young patients.

**Ethics Committee Approval:** Clinical Research Ethics Committee of University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital (approval number: 56/19; approval date: November 12, 2018).

**Informed Consent:** Informed consent was obtained from the patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – M.A.E., H.Ş., K.G.A.; Design – E.G.O., K.G.A., H.Ş; Supervision – E.G.O., K.G.A, H.Ş.; Materials – T.S., G.U.O.; Data Collection and/or Processing – M.A.E., M.D.A.; Analysis and/or Interpretation – G.U.O., F.A.E., T.S.; Literature Review – T.S., F.A.E.; Writing – M.A.E., E.G.O., M.D.A.; Critical Review – M.D.A., G.U.O., F.A.E.

**Declaration of Interests:** The authors have no conflict of interest to declare.

**Funding:** The authors declared that this study had received no financial support.

## REFERENCES

1. Jennette JC. Rapidly progressive crescentic glomerulonephritis. *Kidney Int*. 2003;63(3):1164-1177. [CrossRef]
2. Andrassy K, Küster S, Waldherr R, Ritz E. Rapidly progressive glomerulonephritis: analysis of prevalence and clinical course. *Nephron*. 1991;59(2):206-212. [CrossRef]
3. Hénique C, Papista C, Guyonnet L, Lenoir O, Tharaux PL. Update on crescentic glomerulonephritis. *Semin Immunopathol*. 2014;36(4):479-490. [CrossRef]
4. Moroni G, Ponticelli C. Rapidly progressive glomerulonephritis: early treatment is a must. *Autoimmun Rev*. 2014;13(7):723-729. [CrossRef]

5. Walters GD, Willis NS, Craig JC. Interventions for renal vasculitis in adults: a systematic review. *BMC Nephrol*. 2010;11:12. [CrossRef]
6. Wu T, Peng J, Meng T, et al. Clinicopathological features and prognostic analysis of 49 cases with crescentic glomerulonephritis. *Exp Ther Med*. 2019;18(5):3984-3990. [CrossRef]
7. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int Suppl*. 2012;2(2):139-274.
8. Yates M, Watts RA, Bajema IM, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Ann Rheum Dis*. 2016 ;75(9):1583-1594. [CrossRef]
9. Couser WG. Rapidly progressive glomerulonephritis: classification, pathogenetic mechanism and therapy. *Am J Kidney Dis*. 1988;11(6):449-464. [CrossRef]
10. Levy JB, Hammad T, Coulthart A, Dougan T, Pusey CD. Clinical features and outcome of patients with both ANCA and anti-GBM antibodies. *Kidney Int*. 2004;66(4):1535-1540. [CrossRef]
11. Sanavi S, Afshar R. An unusual presentation of antineutrophil cytoplasmic antibody-associated vasculitis: discrepancy between histopathology and clinical presentation. *Iran J Kidney Dis*. 2011;5(5):347-350.
12. Shah MK, Hugghins SY. Characteristics and outcomes of patients with Goodpasture's syndrome. *South Med J*. 2002;95(12):1411-1418.
13. Derebail VK, Falk RJ. ANCA-associated vasculitis - refining therapy with plasma exchange and glucocorticoids. *N Engl J Med*. 2020;382(7):671-673. [CrossRef]
14. Hildebrand AM, Huang SH, Clark WF. Plasma exchange for kidney disease: what is the best evidence? *Adv Chronic Kidney Dis*. 2014;21(2):217-227. [CrossRef]
15. Walsh M, Merkel PA, Peh CA, et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. *N Engl J Med*. 2020;382(7):622-631. [CrossRef]
16. Gallagher H, Kwan JT, Jayne DR. Pulmonary renal syndrome: a 4-year, single center experience. *Am J Kidney Dis*. 2002;39(1):42-47. [CrossRef]
17. Rutgers A, Slot M, van Paassen P, van Breda Vriesman P, Heeringa P, Tervaert JW. Coexistence of anti-GBM antibodies and myeloperoxidase-ANCAs in crescentic glomerulonephritis. *Am J Kidney Dis*. 2005;46(2):253-262. [CrossRef]
18. Levy JB, Turner AN, Rees AJ, Pusey CD. Long-term outcome of anti-glomerular basement membrane antibody disease treated with plasma exchange and immunosuppression. *Ann Intern Med*. 2001;134(11):1033-1042. [CrossRef]
19. Lee T, Gasim A, Derebail VK, et al. Predictors of treatment outcomes in ANCA-associated vasculitis with severe kidney failure. *Clin J Am Soc Nephrol*. 2014;9(5):905-913. [CrossRef]
20. Salmela A, Törnroth T, Poussa T, Ekstrand A. Prognostic factors for survival and relapse in ANCA-associated vasculitis with renal involvement: a clinical long-term follow-up study. *Int J Nephrol*. 2018;2018:6369814. [CrossRef]
21. Aydın Z, Turkmen K, Dede F, et al. Demographic, clinical and laboratory characteristics of rapidly progressive glomerulonephritis in Turkey: Turkish Society of Nephrology-Glomerular Diseases (TSN-GOLD) Working Group. *Clin Exp Nephrol*. 2021;25(2):173-183. [CrossRef]
22. Cohen BA, Clark WF. Pauci-immune renal vasculitis: natural history, prognostic factors, and impact of therapy. *Am J Kidney Dis*. 2000;36(5):914-924. [CrossRef]
23. Ozturk R, Yenigun EC, Dede F, et al. Prognostic factors in crescentic glomerulonephritis: a single-center experience. *Iran J Kidney Dis*. 2015;9(1):31-38.
24. Jayne DR, Marshall PD, Jones SJ, Lockwood CM. Autoantibodies to GBM and neutrophil cytoplasm in rapidly progressive glomerulonephritis. *Kidney Int*. 1990;37(3):965-970. [CrossRef]
25. Tanna A, Guarino L, Tam FWK, et al. Long-term outcome of anti-neutrophil cytoplasm antibody-associated glomerulonephritis: evaluation of the international histological classification and other prognostic factors. *Nephrol Dial Transplant*. 2015;30(7):1185-1192. [CrossRef]
26. Li FK, Tse KC, Lam MF, et al. Incidence and outcome of antiglomerular basement membrane disease in Chinese. *Nephrology*. 2004;9(2):100-104. [CrossRef]
27. Jeffrey RF, Gardiner DS, More IA, Junor BJ, Briggs JD. Crescentic glomerulonephritis: experience of a single unit over a five year period. *Scott Med J*. 1992;37(6):175-178. [CrossRef]