ARAŞTIRMA MAKALESİ/ORIGINAL RESEARCH

DOI: 10.5505/ktd.2022.98475
Kocaeli Med J 2022;11(2):122-129

Biomarkers of Renal and Overall Survival in Patients with Granulomatosis Polyangiitis

Granülomatoz Polianjitis Hastalarında Renal ve Genel Sağkalımın Biyobelirteçleri

Eray Eroğlu[1]

[1] Kilis State Hospital, Department of Nephrology, Kilis, Turkey

ABSTRACT

Introduction: Granulomatosis with polyangiitis (GPA) is a kind of small blood vessel vasculitis that is characterized by lung and renal involvement with a high mortality rate. This study was aimed to investigate the association of baseline laboratory,demographic, clinical parameters between renal and overall survival in patients with GPA.

Methods: Twenty-four patients diagnosed with GPA between 2010 and 2020 from a tertiary hospital were analyzed retrospectively. Baseline hematological and biochemical parameters, C reactive protein (CRP), and antineutrophil cytoplasmic antibodies (ANCA) were also recorded. History of plasmapheresis and acute dialysis were recorded. Primary endpoints were defined as the diagnosis of end-stage kidney disease and mortality.

Results: Mean age of patients were 53,00±13,78. Ten (41,7%) of 24 patients were male. Median estimated glomerular filtration (eGFR) rate was 62 ml/min/1,73m2 (22,50-88,75).C-ANCA was positive in 15 (65%) patients. Median proteinuria level was 1,30 gr/day (0,80-2,05). Median CRP level was 14,00 g/dl at baseline (4,58-96,80). Cox regression analysis with the adjusted model by age and gender showed that platelet count, eGFR, proteinuria, and CRP levels were significantly associated with renal survival and hemoglobin levels were also associated with overall survival. Platelet count below 150 103/µL and hemoglobin levels below 12 g/dL showed the worst prognosis in terms of renal and overall survival.

Discussion and Conclusion: The platelet count and hemoglobin level could be useful in predicting renal and overall survival at the baseline assessment of patients with granulomatosis polyangiitis.

Keywords: granulomatosis with polyangiitis, platelet, hemoglobin

ÖZ

Giriş ve Amaç: Granülomatozis polianjitis (GPA), akciğer ve böbrek tutulumu ile karakterize, yüksek mortalite oranıyla seyreden bir tür küçük damar vaskülitidir. Bu çalışmanın amacı, GPA'lı hastalarda renal ve genel sağkalım arasındaki temel laboratuvar, demografik, klinik parametrelerin ilişkisini araştırmaktır.

Yöntem ve Gereçler: Üçüncü basamak bir hastanede 2010-2020 yılları arasında GPA tanısı almış 24 hasta geriye dönük olarak incelendi. Temel hematolojik ve biyokimyasal parametreler, C reaktif protein (CRP) ve antinötrofil sitoplazmik antikorlar (ANCA) da kaydedildi. Plazmaferez ve akut diyaliz öyküsü kaydedildi. Birincil son noktalar, son dönem böbrek hastalığı ve mortalite tanısıolarak tanımlandı.

Bulgular: THastaların ortalama yaşı 53,00±13,78 idi. 24 hastanın 10'u (%41,7) erkekti. Medyan tahmini glomeruler filtrasyon hızı (tGFH) 62 ml/dk/1,73m2 (22,50-88,75) idi. 15 (%65) hastada C-ANCA pozitifti. Medyan proteinüri düzeyi 1,30 gr/gün (0,80-2,05) idi. Medyan CRP seviyesi başlangıçta 14,00 g/dl (4,58-96,80) idi. Yaşa ve cinsiyete göre düzeltilmiş model ile yapılan Cox regresyon analizi, trombosit, tGFH, proteinüri ve CRP düzeylerinin böbrek sağkalımı ile önemli ölçüde ilişkili olduğunu ve hemoglobin düzeylerinin de genel sağkalım ile ilişkili olduğunu gösterdi. 150 103/µL'nin altındaki trombosit seviyesi, renal sağkalım açısından en kötü prognozu gösterdi.12 g/dL'nin altındaki hemoglobin seviyesi, genel sağkalım açısından en kötü prognozu gösterdi.

Tartışma ve Sonuç: Granülomatozis polianjitisi olan hastalar için renal ve genel sağkalımı öngörmede başlangıç trombosit ve hemoglobin seviyesinin değerlendirilmesi yararlı olabilir.

Anahtar Kelimeler: granulomatozis polianjitis, trombosit, hemoglobin

Kabul Tarihi: 11.03.2022

Correspondence: Eray Eroğlu, Department of Nephrology, Kilis State Hospital, Kilis, Turkey.
E-mail: drerayeroglu@hotmail.com

Kocaeli Medical Journal published by Cetus Publishing.

INTRODUCTION

Granulomatosis with polyangiitis (GPA), previously named Wegener's granulomatosis, is a kind of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), affecting small and medium sized blood vessels. The characteristic involvements are vasculitis, granulomatous inflammation in affected or- gans, and pauci-immune necrotizing glomerulonephritis. (1). Approximately, 80% of GPA patients are diagnosed with the presence of cytoplasmic-ANCA (c-ANCA) which is occurred against serine protease proteinase 3 (PR3-ANCA) (2). However, 20 to 30 percent of cases with GPA have the perinuclear-ANCA (p-ANCA), and at least 10 percent of cases are negative for ANCA (3,4). The estimated prevalence of granulomatosis with polyangiitis (GPA) is between 20 to 150 cases/million, with an in-cidence of 0,5 to 12 cases/million (5). Therefore, a negative ANCA result does not exclude the diagnosis of GPA. The diagnosis of GPA is established by the assessment of characteristic findings, laboratory tests, imaging studies, and histopathological biopsy results (6).

GPA is a relapsing disease and long-term survival has recently improved since the application of immunosuppressive agents such as rituximab and cyclophosphamide. Currently the ten-year survival of GPA patients is approximately 75% (7). The etiology of the GPA has not completely clarified, however the potential role of genetic and environmental factors has been investigated (8). Several biomarkers and disease activity scoring methods have been proposed in terms of predicting prognosis, although there is not any established prediction tool or biomarker yet (7,9,10). Therefore, the discovery of easily accessible biomarker/s that predict prognosis in GPA has been a challenge.

The purpose of this study was to evaluate commonly measured laboratory parameters and potential predictors of renal and overall survival in patients with GPA.

MATERIAL AND METHODS

Study Population

Twenty-four patients who had been diagnosed with GPA between 2010 and 2020 in Erciyes University Faculty of Medicine Hospital Nephrology department were included for the study. The study was conducted using patients' medical records and the hospital database. The diagnosis of GPA was established in accordance with the Chap- el-Hill nomenclature in all patients (6). The study was approved by the hospital ethics committee. Patients were required to have evidence of renal or lung involvement that is proven by histopathological examination to be eligible for the inclusion criteria. Test results for these biomarkers were recorded for each patient: c-ANCA, p-ANCA, anti-MPO antibody, anti-PR3 antibody, complete blood counting, serum creatinine, and CRP levels. Complete blood cell counts were studied on automated equipment (Sysmex XE-2000). Serum creatinine levels measured by using the Hitachi-747 analyzer. Serum CRP values were measured by Behring BN2 nephelometer. Perinuclear and cytoplasmic staining pattern on ANCA indirect immunofluorescence (IIF) were performed by enzyme-linked immunosorbent assay (ELISA). For ANCA IIF, serum samples were diluted 1/20 and examined using INOVA neutrophil coated slides. Anti-PR3 antibody and anti-MPO antibody levels were measured using the Biodiagnostics ELISA system. Estimated glomerular filtration rate (eGFR) was calculated by using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (11). The administration of acute dialysis and plasmapheresis were also recorded. Primary endpoints were defined as the diagnosis of end stage kidney disease and mortality as renal and overall survival respectively.

Statistical Analysis

Histogram, q-q plots were plotted, and Shapiro-Wilk's test was used to assess the data normality. Continuous variables were summarized as mean and standard deviation or median and interquartile ranges depending on the data distribution. Categorical variables were summarized as frequencies and percentages. Survival probabilities were estimated with the Kaplan–Meier method and compared between groups using the log-rank test. Furthermore, univariate Cox regression analysis was used to assess the risk of clinical variables on renal and overall survival. Both crude and age, gender adjusted models were provided. Hazard ratios are calculated with 95% confidence intervals. *p* values less than 5% are considered as statistically significant. All analyses are conducted using R 3.5.1 (www.r-project.org) and TURCOSA (Turcosa Analytics Ltd. Co., Turkey, www.turcosa.com.tr) software.

RESULTS

The demographic, clinical and laboratory characteristics of the study population are shown in Table-1. Mean age of patients was 53,00±13,78 and 10 of 24 patients (41,7%) were male. Median eGFR was 62 ml/min/1,73m2 (22,50-88,75). C-ANCA was positive in 15 (65%) patients. 5 patients (21,7%) were ANCA negative Median proteinuria level was 1,30 gr/day (0,80-2,05). Median hemoglobin levels were 12,49±2,24 g/dL and median platelet count were 222,71±113,42 10^3/µL. Median CRP level was 14,00 g/dl at baseline (4,58-96,80).

Binary cox regression analysis was performed for predicting renal and overall survival (**Table-2**). Platelet count, e-GFR, proteinuria and acute dialysis initiation were significant factors predicting renal survival in adjusted model for age and gender. Platelet count below 150 10^3/µL led to a 12,69-fold increase in the risk of ESRD development (95%CI:1,98-81,35), *p*=0,007. Each unit of increase in eGFR led to a 0.95-fold decrease in the risk of ESRD development (95% CI: (0,91-0,99), *p*=0,015. Each unit of increase in proteinuria led to a 2,52-fold increase in the risk of ESRD development (95% CI: 1,12-5,65), *p*=0,025. Acute dialysis initiation presence led to a 23,74-fold increase the risk of ESRD development (95% CI: 2,29-245.93), *p*=0,008. In terms of overall survival, hemoglobin level was the only significant factor for predicting mortality in adjusted model for age and gender. Hemoglobin level below 12 g/dL led to a 19,69-fold increase in the risk of ESRD development (95%CI:1,57-246,22), p=0,021.

Table 1. Demographical, Clinical and Laboratory Characteristics of Patients

Variable	Patients (n=24)
Age (years)	53,00±13,78
Gender (male) (%)	10(41,7)
White blood cell (mm3/µL)	7,87(5,96-11,08)
Hemoglobin (g/dL)	12,49±2,24
Platelets (10^3/µL)	222,71±113,42
Glucose (mg/dL)	93,50(85,50-151,00)
BUN (mg/dL)	26,00(17,33-43,30)
Creatinine (mg/dL)	1,19(0,88-2,55)
eGFR (ml/min/1,73m²)	62,00(22,50-88,75)
Uric acid (mg/dL)	5,40±1,62
Sodium (mmol/L)	139,13±4,12
Potassium (mmol/L)	4,42±0,62
ANCA	
Negative	5(21,7)
c-ANCA+	15(65,2)
p-ANCA+	3(13,0)
MPO and PR3	
Negative	4(16,7)
MPO	3(12,5)
PR-3	17(70,8)
Proteinuria (g/day)	1,30(0,80-2,05)
CRP (mg/L)	14,00(4,58-96,80)

Values are expressed as n(%), mean±SD or median(1st-3rd quartiles), BUN: Blood urea nitrogen, CRP: C- reactive protein, ANCA: Antineutrophil cytoplasmic autoantibodies, c-ANCA: Cytoplasmic-antineutrophil cytoplasmic antibody, p-ANCA: Perinuclear-antineutrophil cytoplasmic antibody, MPO: Myeloperoxidase , PR-3 :Proteinase 3

Table 2. Binary Cox Regression Analysis Results in Predicting Renal and Overall Survival in Patients with Granulomatosis Polyangiitis

Variables	Renal Survival				Overall Survival			
	Crude		Adjusted*		Crude		Adjusted*	
	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p
Age (years)	1,01(0,96-1,06)	0,819	-	-	1,02(0,96-1,08)	0,577	-	-
Gender (male/ female)	2,81(0,66-11,89)	0,160	-	-	2,97(0,56-15,81)	0,203	-	-
White blood cell (mm3/µL)	0,94(0,76-1,15)	0,528	0,92(0,73-1,16)	0,475	1,04(0,85-1,27)	0,687	1,04(0,85-1,28)	0,704
Hemoglobin (g/dL)	0,73(0,55-0,98)	**0,037**	0,77(0,53-1,12)	0,171	0,78(0,58-1,05)	0,098	0,78(0,52-1,19)	0,253
Hemoglobin (<12g/dL/ ≥12g/dL)	4,43(1,04-18,93)	**0,044**	3,54(0,65-19,39)	0,145	13,96(1,65-118,54)	**0,016**	19,69(1,57-246,22)	**0,021**
Platelets (10^3/µL)	0,99(0,98-0,99)	**0,005**	0,98(0,96-0,99)	**0,022**	0,98(0,97-0,99)	**0,026**	0,99(0,97-1,00)	0,080
Platelets (<150 10^3/µL/≥150 10^3/µL)	11,34(2,24-57,50)	**0,003**	12,69(1,98-81,35)	**0,007**	5,88(1,09-31,80)	**0,040**	5,08(0,78-32,95)	0,088
Glucose (mg/dL)	1,00(0,99-1,01)	0,649	0,99(0,98-1,01)	0,772	1,00(0,99-1,02)	0,560	1,00(0,99-1,02)	0,550
BUN (mg/dL)	1,03(1,01-1,07)	**0,046**	1,03(0,99-1,07)	0,160	1,01(0,98-1,05)	0,499	1,00(0,96-1,05)	0,945
Creatinine (mg/dL)	1,24(1,04-1,49)	**0,018**	1,20(0,98-1,48)	0,079	0,88(0,60-1,29)	0,507	0,74(0,41-1,35)	0,331
eGFR (ml/ min/1,73m^2)	0,95(0,91-0,99)	**0,023**	0,95(0,91-0,99)	**0,015**	1,00(0,97-1,02)	0,863	1,01(0,98-1,04)	0,618
Uric acid (mg/dL)	1,11(0,68-1,81)	0,686	1,09(0,63-1,87)	0,761	0,85(0,50-1,45)	0,546	0,81(0,45-1,46)	0,479
Proteinuria (g/day)	2,13(1,11-4,09)	**0,023**	2,52(1,12-5,65)	**0,025**	0,99(0,45-2,17)	0,987	0,94(0,37-2,35)	0,886
CRP (mg/L)	1,01(1,00-1,02)	**0,028**	1,01(0,99-1,02)	0,155	1,01(1,00-1,02)	**0,019**	1,02(1,00-1,04)	0,051
Acute dialysis (present/absent)	18,64(2,27-153,27)	**0,007**	23,74(2,29-245,93)	**0,008**	2,10(0,43-10,21)	0,359	1,35(0,21-8,56)	0,749
Plasma exchange (present/absent)	0,61(0,07-5,10)	0,651	0,50(0,06-4,30)	0,525	0,57(0,06-5,17)	0,615	0,62(0,07-5,61)	0,669
ANCA (p-ANCA+ /c-ANCA+)	0,67(0,08-5,81)	0,716	0,69(0,08-6,34)	0,741	0,62(0,06-6,00)	0,682	0,56(0,05-6,38)	0,638

**Adjusted by age and gender, HR: Hazard ratio, CI: Confidence interval, All significant variables are shown in bold, BUN: Blood urea nitrogen, CRP: C- reactive protein, ANCA: Antineutrophil cytoplasmic autoantibodies, c-ANCA: Cytoplasmic-antineutrophil cytoplasmic antibody, p-ANCA: Perinuclear-antineutrophil cytoplasmic antibody,*

Mean renal survival was 60,75±31,19 months. Mean overall survival was 66,75 ±31,18 months. Overall survival curves with hemoglobin level <12 g/dL vs ≥12 g/dL and renal survival curves with platelet count <150 10^3/µL vs ≥ 150 10^3/µL were compared using the Kaplan-Meier survival analysis in study pa- tients. Patients with hemoglobin level <12 g/ dL had a shorter renal survial (46 months vs 66 months) (log-rank test, p=0.029) and overall survival (53 months vs 72 months) (log-rank test, p=0.00201) compared to those with hemoglobin level ≥12 g/dL (**Figure-1**). Patients with platelet count <150 10^3/µL had a shorter renal survival (38 months vs 68 months) (log-rank test, p=0,000317) and overall survival (58 months vs 70 months) (log-rank test, p=0,0226) compared to those with platelet count ≥150 10^3/µL (**Figure-2**).

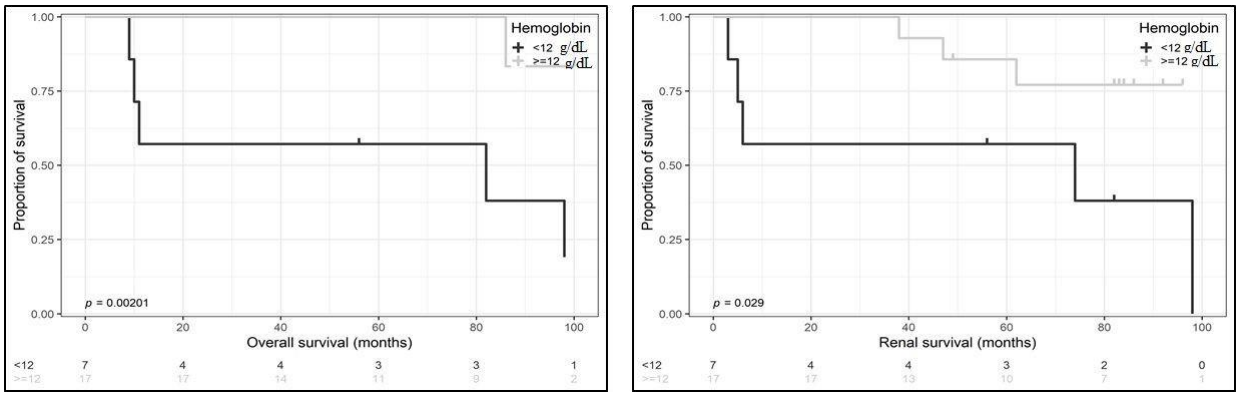

Figure 1. Comparison of Patients according to the Hemoglobin Level in terms of Renal/Overall Survival

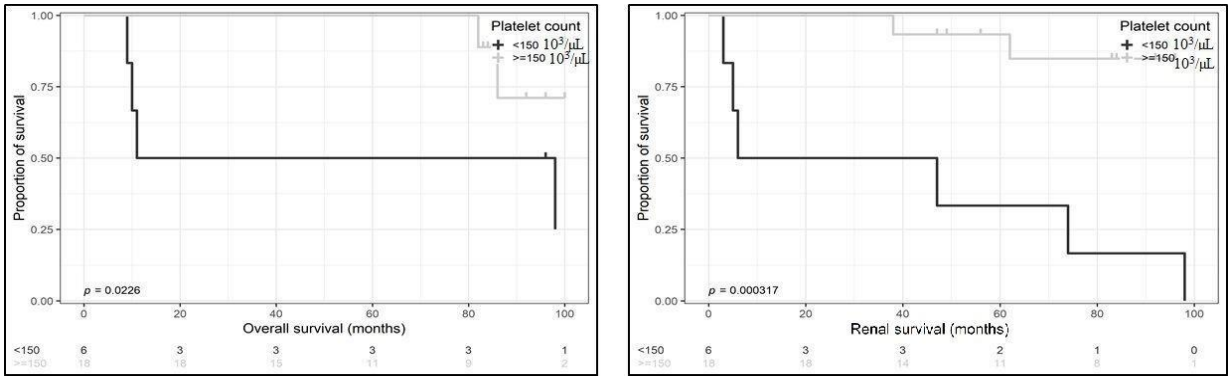

Figure 2. Comparison of Patients according to the Platelet Count in terms of Renal/Overall Survival

DISCUSSION

This study proposes three major findings for predicting renal and overall survival in patients with GPA. Decreased hemoglobin levels could be associated with the overall survival and low platelet count could be useful in predicting renal survival in patients with GPA independently from age and gender. In addition, initial renal dysfunction requiring acute dialysis could be a clinical harbinger of ESRD development in these patients.

Kidney involvement is one of the common problems in patients with GPA. The studies from the National Institutes of Health (NIH) in the United States revealed that evident glomerulonephritis was present in only 18 percent of patients at presentation, however it subsequently developed in 77 to 85 percent of patients, mostly within the first two years of disease onset (12,13). The typical clinical presentation of kidney involvement is rapidly progressive glomerulonephritis. Hematuria, subnephrotic proteinuria and renal dysfunction could be detected at the initial diagnosis with different degrees. Renal biopsy findings usually consistent with the pauci-immune crescentic glomerulonephritis (1). In this study, the patients had slightly renal dysfunction at the first hospital visit with median eGFR was 62.00 ml/min/1,73^2. Mean proteinuria level was 1,30 gr/24 h consistent with the current literature. All patients had microscopic hematuria and 19 of 24 patients diagnosed with crescentic glomerulonephritis by histopathological evaluation of the patients' kidney biopsy. There is not enough knowledge about the biomarkers predicting renal survival in patients with GPA, thus this study aimed primary end point as the diagnosis of ESRD for renal survival. In line with the current literature, the initial degree of

renal dysfunction and requirement of acute dialysis predicted renal survival (12,14). On the other hand, the present study showed a new finding that may add the current literature that low platelet count (<150 10^3/μL) could be a harbinger of renal survival. However pathological mechanism is unclear, it could be speculated that the vascular endothelial damage in glomeruli may decrease platelet count which addresses new investigations in patients with GPA. Interestingly there was no increased risk with patients positive c-ANCA versus p-ANCA in terms of renal survival. The possible explanation for this result that it has been included only one value at baseline. However, serial measurements, and titers of c-ANCA and anti-PR3 might be associated with prognosis. Although, Finkelman et al. (15) proposed that ANCA levels cannot used to manage immunosuppressive treatment, Kerr et al. (16) demonstrated that an increase in c-ANCA titer predicted the clinical exacerbation of disease in only patients with GPA. However subsequent study by Boomsma et al. (17) recommended a serial measurement of ANCA levels could beuseful in the early prediction of disease relapse. Hogan et al. showed that combined of CRP, neutrophil count with anti-PR-3 antibody seropositivity could also predict relapses (9,18).

The mortality rate of untreated GPA patients is approximately 90% within two years. The long-term survival in patients with GPA has improved drastically due to the administration of rituximab or cyclophosphamide in therapeutic regimen combinations (19). However, patients with GPA still have a higher mortality rate compared with the general population (19). A meta-analysis of observational studies of patients with GPA reported a 2,7-fold increased risk of mortality compared to the general population (21). The major causes of mortality in patients with GPA are complications of immunosuppressive treatment such as infections(22), complications of the GPA (eg, kidney failure, pulmonary failure), and cardiovascular disease (23,24). However, there is not enough knowledge about prediction of mortality by biomarkers, thus the present study aimed to investigate potential easily accessible biomarker for this purpose. This study showed that patients with low levels of hemoglobin at baseline (<12 g/dL) had increased mortality compared to patients with normal levels of he- moglobin (≥12 g/dL). Possible causes of low hemoglobin levels are the decreasing erythrocyte count due to inflammation, decreased level of erythropoietin due to renal dysfunction or possible hemorrhages in lung or other tissues. Thus, low level of hemoglobin may be the harbinger of severe disease that could be useful determining severe form of GPA patients.

However, some limitations could be addressed for this study. The low number of patients and the retrospective study design are the main limitations. Further prospective studies in large populations are needed to investigate predictive markers of GPA. Thirdly, the level of ANCAs were measured only once.

In conclusion, GPA patients with renal dysfunction that requiring hemodialysis, low platelet count and low levels of hemoglobin had the worst prognosis. Physicians should consider these parameters identifying high risk patients with GPA.

Ethics Committee Approval: Erciyes University Clinical Research Ethics Committee (: date:12.06.2019 and no:2019/440)
Authors' contributions: E.E. designed the study, collected the data, performed analysis and wrote the paper
Conflict of Interest: There is no conflict of interest.
Funding: There is no financial support.
Informed Consent: This study was conducted with a retrospective design.

REFERENCES

1. Almaani S, Fussner LA, Brodsky S, Meara AS, Jayne D. Clinical Medicine ANCA-Associated Vasculitis: An Update. J Clin Med [Internet]. 2021;10. Available from: https://doi.org/10.3390/jcm10071446
2. Finkielman JD, Lee AS, Hummel AM, Viss MA, Jacob GL, Homburger HA, et al. ANCA Are Detectable in Nearly All Patients with Active Severe Wegener's Granulomatosis. The American Journal of Medicine [Internet]. 2007 Jul 1 [cited 2022 Jan 27];120(7):643.e9-643.e14. Available from: http://www.amjmed.com/article/S0002934306009697/fulltext
3. Hagen EC, Daha MR, Hermans J, Andrassy K, Csernok E, Gaskin G, et al. Diagnostic value of standardized assays for anti-neutrophil cytoplasmic antibodies in idiopathic systemic vasculitis. EC/BCR Project for ANCA Assay Standardization. Kidney Int [Internet]. 1998 [cited 2022 Jan 27];53(3):743–53. Available from:https://pubmed.ncbi.nlm.nih.gov/9507222/
4. Savige J, Pollock W, Trevisin M. What do antineutrophil cytoplasmic antibodies (ANCA) tell us? Best Pract Res Clin Rheumatol [Internet]. 2005 [cited 2022 Jan 27];19(2):263–76. Available from: https://pubmed.ncbi.nlm.nih.gov/15857795/
5. Kitching AR, Anders HJ, Basu N, Brouwer E, Gordon J, Jayne DR, et al. ANCA-associated vasculitis. Nat Rev Dis Primers [Internet]. 2020 Dec 1 [cited 2022 Jan 27];6(1). Available from: https://pubmed.ncbi.nlm.nih.gov/32855422/
6. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum [Internet]. 2013 Jan [cited 2022 Jan 27];65(1):1–11. Available from: https://pubmed.ncbi.nlm.nih.gov/23045170/
7. Banerjee P, Jain A, Kumar U, Senapati Sabyasachi. Epidemiology and genetics of granulomatosis with polyangiitis. 2021 [cited 2022 Jan 27];41:2069–89. Available from: https://doi.org/10.1007/s00296-021-05011-1
8. Alberici F, Martorana D, Vaglio A. Genetic aspects of anti-neutrophil cytoplasmic antibody- associated vasculitis. Nephrol Dial Transplant [Internet]. 2015 Sep 30 [cited 2022 Jan 27];30 Suppl 1:i37–45. Available from: https:// pubmed.ncbi.nlm.nih.gov/25523449/
9. Hogan PCP, O'Connell RM, Scollard S, Browne E, Hackett EE, Feighery C. Biomarkers Predict Relapse in Granulomatosis with Polyangiitis. J Biomark [Internet]. 2014 Apr 30 [cited 2022 Jan 27];2014:1–4. Available from: https://pubmed. ncbi.nlm.nih.gov/26317035/
10. Land J, Abdulahad WH, Arends S, Sanders JSF, Stegeman CA, Heeringa P, et al. Prospective monitoring of in vitro produced PR3-ANCA does not improve relapse prediction in granulomatosis with polyangiitis. PLoS ONE. 2017 Aug 1;12(8).
11. Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med [Internet]. 2009 May 5 [cited 2022 Jan 27];150(9):604–12. Available from: https://pubmed.ncbi.nlm.nih.gov/19414839/
12. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med [Internet]. 1992 [cited 2022 Jan 27];116(6):488–98. Available from: https://pubmed.ncbi.nlm.nih.gov/1739240/
13. Fauci AS, Haynes BF, Katz P, Wolff SM. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. Ann Intern Med [Internet]. 1983 [cited 2022 Jan 27];98(1):76–85. Available from: https://pubmed.ncbi.nlm.nih.gov/6336643/
14. Slot MC, Cohen Tervaert JW, Franssen CFM, Stegeman CA. Renal survival and prognostic factors in patients with PR3-ANCA associated vasculitis with renal involvement. Kidney Int [Internet]. 2003 [cited 2022 Jul 19];63(2):670–7. Available from: https://pubmed.ncbi.nlm.nih. gov/12631133/
15. Finkielman JD, Merkel PA, Schroeder D, Hoffman GS, Spiera R, st. Clair EW, et al. Antiproteinase 3 antineutrophil cytoplasmic

antibodies and disease activity in Wegener granulomatosis. Ann Intern Med [Internet]. 2007 Nov 6 [cited 2022 Jan 27];147(9):611–9. Available from: https://pubmed.ncbi.nlm.nih.gov/17975183/

16. Kerr GS, Fleisher TA, Hallahan CW, Leavitt RY, Fauci AS, Hoffman GS. Limited prognostic value of changes in antineutrophil cytoplasmic antibody titer in patients with Wegener's granulomatosis. Arthritis Rheum [Internet]. 1993 [cited 2022 Jan 27];36(3):365–71. Available from: https://pubmed.ncbi.nlm.nih.gov/8452581/
17. Boomsma MM, Stegeman CA, van der Leij MJ, Oost W, Hermans J, Kallenberg CGM, et al. Prediction of relapses in Wegener's granulomatosıs by measurement of antineutrophil cytoplasmic antibody levels a prospective study. Arthritis & Rheumatism. 2000;43(9):2025–33.
18. Hogan SL, Falk RJ, Chin H, Cai J, Jennette CE, Jennette JC, et al. Predictors of relapse and treatment resistance in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis. Ann Intern Med [Internet]. 2005 Nov 1 [cited 2022 Jan 27];143(9). Available from: https://pubmed.ncbi.nlm.nih.gov/ 16263884/
19. Wallace ZS, Lu N, Miloslavsky E, Unizony S, Stone JH, Choi HK. Nationwide Trends in Hospitalizations and In-Hospital Mortality in Granulomatosis With Polyangiitis (Wegener's). Arthritis Care Res (Hoboken) [Internet]. 2017 Jun 1 [cited 2022 Jan 27];69(6):915–21. Available from: https://pubmed.ncbi.nlm.nih.gov/27389595/
20. Tan JA, Choi HK, Xie H, Sayre EC, Esdaile JM, Aviña-Zubieta JA. All-Cause and Cause-Specific Mortality in Patients With Granulomatosis With Polyangiitis: A Population-Based Study. Arthritis Care Res (Hoboken) [Internet]. 2019 Jan 1 [cited 2022 Jan 27];71(1):155–63. Available from: https://pubmed.ncbi.nlm.nih.gov/29692001/
21. Tan JA, Dehghan N, Chen W, Xie H, Esdaile JM, Avina-Zubieta JA. Mortality in ANCA-associated vasculitis: ameta-analysis of observational studies. Ann Rheum Dis [Internet]. 2017 Sep 1 [cited 2022 Jan 27];76(9):1566–74. Available from: https:// pubmed.ncbi.nlm.nih.gov/ 28468793/
22. Lionaki S, Hogan SL, Jennette CE, Hu Y, Hamra JB, Jennette JC, et al. The clinical courseof ANCA small-vessel vasculitis on chronic dialysis. Kidney Int [Internet]. 2009 Sep [cited 2022 Jan 27];76(6):644–51. Available from: https://pubmed.ncbi.nlm.nih.gov/19536079/
23. Robson J, Doll H, Suppiah R, Flossmann O, Harper L, Höglund P, et al. Damage in the anca-associated vasculitides: long-term data from the European vasculitis study group (EUVAS) therapeutic trials. Ann Rheum Dis [Internet]. 2015 Jan 1 [cited 2022 Jan 27];74(1):177–84. Available from: https://pubmed.ncbi.nlm.nih.gov/24243925/
24. Lai QY, Ma TT, Li ZY, Chang DY, Zhao MH, Chen M. Predictors for mortality in patients with antineutrophil cytoplasmic autoantibody-associated vasculitis: a study of 398 Chinese patients. J Rheumatol [Internet]. 2014 [cited 2022 Jan 27];41(9):1849–55. Available from: https://pubmed.ncbi.nlm.nih.gov/25086076/
25.