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MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

Clinicopathological and Prognostic Study in Patients with Crescentic Glomerulonephritis: A Thirteen Year Single Center Experience

Kresentik Glomerülonefritli Hastalarda Klinikopatolojik ve Prognostik Çalışma: On Üç Yıllık Tek Merkez Deneyimi

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Abstract

Objectives: Various risk factors associated with crescentic glomerulonephritis (CGN) prognosis have been reported, but there is no definitive consensus for prognostic predictors of kidney outcome. We aimed to investigate the factors associated with developing end-stage kidney disease (ESKD) in CGN patients.

Materials and Methods: Over 13 years, we retrospectively evaluated kidney biopsy results, clinical, and laboratory data of patients diagnosed with CGN at our center. The relationships between potential predictors and kidney outcomes were investigated.

Results: We analyzed 91 patients diagnosed with CGN. The mean age was 46.4±17.4 years, and 59% were male. Over a median follow-up of 17 months, 34 (37%) patients resulted in ESKD, and 12 (13%) patients died. Cox regression analysis showed that the serum creatinine level was above 3 mg/dL at the time of diagnosis, requirement for dialysis, presence of more than 24% globally sclerotic glomeruli on kidney biopsy, and >25% interstitial fibrosis and tubular atrophy (IFTA) score were found to be associated with ESKD. On multivariate analysis, need for dialysis [hazard ratio (HR): 2.4, 95% confidence interval (CI): 1.06-5.40, p=0.034], the serum creatinine level >3 mg/dL (HR: 2.92, 95% CI: 1.05-8.10, p=0.040), and IFTA score >25% (HR: 2.85, 95% CI: 1.31-6.20, p=0.008) were independent risk factors for the development of ESKD.

Conclusion: Chronic changes in kidney biopsy and the severity of kidney function impairment provide helpful information for predicting kidney outcomes in patients with CGN. Early diagnosis and appropriate therapy are of the utmost importance to improve the prognosis of patients with CGN.

Keywords: Crescentic glomerulonephritis, end-stage kidney disease, kidney biopsy, risk factors

Öz

Amaç: Kresentik glomerülonefrit (KGN) prognozu ile ilişkili çeşitli risk faktörleri bildirilmiş olsa da, böbrek sağkalımı prognostik beliryecileri için kesin bir fikir birliği yoktur. KGN hastalarında gelişen son dönem böbrek hastalığı (SDBH) ile ilişkili faktörleri araştırmayı amaçladık.

Gereç ve Yöntem: On üç yılı aşkın bir sürede merkezimizde KGN tanısı alan hastaların böbrek biyopsi sonuçlarını, klinik ve laboratuvar verilerini retrospektif olarak değerlendirdik. Potansiyel belirleyiciler ile böbrek sonuçları arasındaki ilişkileri araştırdık.

Bulgular: KGN tanısı alan 91 hastayı inceledik. Yaş ortalaması 46,4±17,4 yıl olup, %59'u erkekti. On yedi aylık medyan takip süresi boyunca, 34 (%37) hasta SDBH ile sonuçlandı ve 12 (%13) hasta öldü. Cox regresyon analizinde, tanı anında serum kreatinin düzeyinin 3 mg/dL'nin üzeri, diyaliz

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gereksinimi varlığı, böbrek biyopsisinde global sklerotik glomerül oranının >%24 ve interstisyel fibrozis ve tübüler atrofi (IFTA) skorunun >%25 olmasının SDBH ile ilişkili olduğu bulundu. Çok değişkenli analizde, diyaliz gereksinimi [risk oranı (HR): 2,4, %95 güven aralığı (GA): 1,06-5,40, p=0,034), serum kreatinin düzeyinin >3 mg/dL (HR: 2,92, %95 GA: 1,05-8,10, p=0,040) ve IFTA skorunun >%25 (HR: 2,85, %95 GA: 1,31-6,20, p=0,008) olması SDBH gelişimi için bağımsız risk faktörleriydi.

Sonuç: Böbrek biyopsisindeki kronik değişiklikler ve böbrek fonksiyon bozukluğunun şiddeti, KGN'li hastalarda böbrek sonuçlarını öngörmede yardımcı bilgiler sağlar. KGN'li hastaların prognozunu iyileştirmek için erken tanı ve uygun tedavi son derece önemlidir.

Anahtar Kelimeler: Kresentik glomerülonefrit, son dönem böbrek hastalığı, böbrek biyopsisi, risk faktörleri

Introduction

Crescentic glomerulonephritis (CGN) describes a group of glomerular diseases characterized by rapid impairment of kidney function and the formation of glomerular crescents, and often referred to as rapidly progressive glomerulonephritis (RPGN) (1). In clinical practice, the widespread definition of CGN is the presence of crescents in more than 50% of glomeruli on kidney biopsy. However, there is no consensus on this issue and adverse kidney prognosis can occur with a lower percentage of crescents (2). In general, biopsies with less than 10 percent of crescents are not referred to as CGN.

Early diagnosis and appropriate therapy are of the utmost importance to improve the prognosis of patients with CGN, because the natural course of CGN usually results in end-stage kidney disease (ESKD) (3). Many studies have shown that various risk factors are associated with the development of ESKD in CGN patients, which include age (4), kidney function at presentation (4,5), underlying glomerular disease (1,5), arteriolar fibrinoid necrosis (6), and the percentage of glomeruli with crescents (7). Chronic histopathologic lesions including globally sclerosed glomeruli and tubulointerstitial fibrosis can also impact the prognosis (5,8-10). In recent years, neutrophil-to lymphocyte ratio and C-reactive protein (CRP)-to-serum albumin ratio have been reported as potential new markers of systemic inflammation to predict outcomes in CGN patients (11,12). Although many clinical and histological factors have been identified to predict kidney prognosis, none of these factors alone are sufficient to predict the prognosis. Yet, to date, the prognosis largely depends on the serum creatinine level at the time of diagnosis (3).

In the present study, we assessed the clinicopathological characteristics of patients with biopsy-proven CGN in our center to determine predictors for the development of ESKD.

Materials and Methods

Study Design and Selection of Patients

Our study was performed in a university hospital and had a retrospective design. A total of 103 patients who underwent native kidney biopsy and whose crescent formation was identified in the biopsy specimen between 2005-2018 were evaluated. Patients with a minimum of 10% crescent in a biopsy specimen, sufficient clinical and laboratory data at the time of diagnosis were included in this study. Baseline data of 12 patients were excluded from this study after the review of histological findings and medical data record. Finally, a total of 91 patients were analyzed.

Ethics Statement

This study protocol was approved by the Ankara University Faculty of Medicine Ethics Committee for Clinical Studies and was in adherence with the Declaration of Helsinki (approval no.: 07-440-18, date: 16.04.2018). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Clinical Characteristics and Laboratory Findings

Clinical and laboratory parameters of all patients were enrolled at the time of kidney biopsy from the hospital database. Age, gender, erythrocyte sedimentation rate, hemoglobin, hematocrit, white blood cell count, neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio, CRP, serum albumin, CRP-to-albumin ratio, serum creatinine, estimated glomerular filtration rate (eGFR), 24-hour urine protein amount or spot urine protein/creatinine ratio, myeloperoxidase-antineutrophil cytoplasmic antibody (ANCA), proteinase 3-ANCA, anti-glomerular basement membrane (GBM) antibody, systolic blood pressure (SBP), diastolic blood pressure (DBP), lipids, presence of hematuria, edema, hypertension, diabetes mellitus, dyslipidemia, the requirement for dialysis at presentation, extrarenal organ involvement, and kidney biopsy indications were recorded.

Definitions

The term of CGN was defined as at least 10% of total crescentic glomeruli in the kidney biopsy (7). The eGFR was calculated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) study equation (13).

The neutrophil-to-lymphocyte ratio is a readily available result from the complete blood count test and was defined as the ratio of neutrophil count to lymphocyte count. The CRP-to-albumin ratio was calculated by dividing the serum CRP level by the serum albumin level. Microscopic hematuria was

defined as three or more red blood cells per high-power field on urine examination. Diabetes mellitus was defined based on the criteria of the American Diabetes Association or the use of medications such as oral hypoglycemic agents and/or insulin (14). Hypertension was defined as a SBP of at least 140 mmHg, and/or a DBP of at least 90 mmHg, and/or previously diagnosed hypertension, and/or the use of antihypertensive medications (15). Dyslipidemia was defined as total serum cholesterol level greater than or equal to 200 mg/dL, or low-density lipoprotein cholesterol above 100 mg/dL, or triglycerides greater than 150 mg/dL, or taking lipid-lowering drugs (16).

Kidney biopsy indications included RPGN, nephrotic syndrome, nephritic syndrome, and asymptomatic urinary abnormalities. ESKD was defined as the need for kidney replacement therapy (dialysis, transplantation). RPGN was defined as progressive loss of kidney function (eGFR <60 mL/min/1.73 m^2) over a very short period of time (days, weeks, or a few months) associated with proteinuria, hematuria (microscopic or macroscopic), decreased urine output, hypertension, and edema. Nephrotic syndrome was defined as the presence of heavy proteinuria (protein excretion greater than 3.5 g/24 hours), hypoalbuminemia (less than 3.5 g/dL), peripheral edema, and eGFR ≥60 mL/min/1.73 m^2. Nephritic syndrome was defined as hematuria, proteinuria (protein excretion <3.5 g/24 hours), hypertension, edema, and eGFR ≥60 mL/min/1.73 m^2. Asymptomatic urinary abnormalities were defined as proteinuria (protein excretion <3.5 g/24 hours) and/or hematuria, without edema, hypertension, and decreased eGFR.

Histopathologic Examination

All slides of the kidney biopsies including hematoxylin and eosin, Masson trichrome, periodic acid Schiff and Jones methenamine silver stained preparations, were reexamined for the elemantary lesions of kidney compartments; glomeruli, tubules, interstitium and vascular structures. Accordingly, mesangial proliferation, endocapillary proliferation, fibrinoid necrosis, sclerosis (segmental/globally) and crescent (cellular/fibrocellular/fibrous) formation for glomerular compartment, interstitial inflammation, interstitial fibrosis and tubular atrophy (IFTA) for tubulointerstitial compartment, and arteriolar hyalinosis, arteriosclerosis and vasculitis for vascular compartment were noted. Total number of glomeruli in each biopsy were recorded. While the mesangial proliferation, endocapillary proliferation, fibrinoid necrosis and vascular changes were assessed as presence or absence, the percentage of the glomeruli with crescents (regardless of the type) was calculated. The percentages of glomeruli with cellular, fibrocellular and fibrous crescents were also calculated seperately according to the relative ratio. Crescent formation was defined as extracapillary proliferation of ≥2 cell layers composed of a variable mixture of cells, occupying >25% of the circumference of Bowman's capsule. Crescents composed of cells usually with fibrin and inflammatory cells were called as cellular crescent, whereas the crescents with mixture of cells and fibrosis, and the crescents composed of predominantly fibrous tissue called as fibrocellular and fibrous, respectively. IFTA was graded on a scale of 0 to 3; 0: nil, grade 1 (mild): <25%, grade 2 (moderate): 25-50% and grade 3 (severe): >50% of the cortical paranchyme.

Immunofluorescence findings and the histopathological diagnosis achieved by the interpretation of light microscopic and immunofluorescence findigs were obtained from the pathology reports.

Follow-up and Outcomes

All therapies received by the patients, including supportive, immunosuppressive and need for dialysis at presentation were obtained from the hospital database. During the follow-up period, the patients were divided into two groups according to their kidney outcomes. Group I (Non-ESKD group) and group II (ESKD group). Patients' characteristics were compared among two groups. Finally, risk factors were assessed to identify the predictors of the development of ESKD. Throughout the entire follow-up period, patients' survival and the causes of death were also recorded.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Science 15.0 software for Windows (SPSS Inc., Chicago, Illinois, USA). The Kolmogorov-Smirnov test was used to assess normal distribution.

Descriptive statistics for continuous variables were presented as the mean ± standard deviation or median (minimum-maximum), and categorical variables were presented as the number of cases or percentile. Categorical variables were examined using the chi-square test or the Fisher's exact test. Differences between groups were analyzed using the Student's t-test for normally distributed variables, the Mann-Whitney U test for non-normally distributed variables, or the chi-square test and Fisher's exact test for categorical variables. The receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cutoff values of global sclerosed glomeruli ratio and serum creatinine level for the prediction of ESKD. The Cox regression analysis was used to identify risk factors that predict ESKD. The variables for which $p<0.20$ was found by univariate analysis were included in the multivariate regression analysis. p values less than 0.05 were considered statistically significant.

Results

The Baseline Characteristics of the Patients and Histopathological Findings

A total of 91 patients diagnosed with CGN were analyzed. The mean age of the study population was 46.4±17.4 years, 54 (59%) were males. The prevalence of hypertension, diabetes mellitus, and dyslipidemia were 45%, 11% and 65%, respectively. At the time of presentation, the mean serum creatinine was 3.5±2.4 mg/dL, eGFR was 34±33 mL/min/1.73 m^2. The vast majority of patients (90%) had microscopic hematuria, while only 10% had macroscopic hematuria. Twenty-one patients (23%) had severe impairment of kidney function requiring dialysis therapy and thirty-five patients (38.5%) had extrarenal organ involvement. The kidney biopsy indications of the patients were as follows: 74 (81%) had RPGN, nine (10%) had nephrotic syndrome, four (4.5%) had nephritic syndrome, and four (4.5%) had asymptomatic urinary abnormalities. In kidney biopsy findings, the median number of total glomeruli, crescentic glomeruli, and globally sclerotic glomeruli were 12 (2-38), 4 (1-31) and 2 (0-27), respectively.

The overall crescentic glomeruli ratio was 43%, cellular crescentic glomeruli ratio was 23%, and globally sclerotic glomeruli ratio was 25%. The underlying diseases of CGN patients were as follows: Seven (7.7%) had anti-GBM glomerulonephritis, 13 (14.3%) had lupus nephritis, 26 (28.6%) had immunoglobulin A nephropathy, four (4.4%) had infection-related glomerulonephritis, one (1%) had membranous glomerulonephritis, and 40 (44%) had ANCA-associated glomerulonephritis. The baseline characteristics of the patients and histopathological findings are shown in Tables 1 and 2.

Differences Between Patients with Non-ESKD and ESKD

Over a median follow-up of 17 months, thirty-four (37%) of the total patients resulted in ESKD and twelve (13%) patients died. The causes of death were infectious complications for six patients, cardiovascular events for four, and gastrointestinal bleeding for two. Follow-up period, SBP, DBP, hemoglobin, hematocrit, and HDL cholesterol all showed significant differences between the groups. The ESKD patients group had a significantly higher rate of prevalence of hypertension (61.7% vs. 35%, p=0.007) and need for dialysis at presentation (50% vs. 7%) than in non-ESKD patients group. We also observed significant differences in baseline mean serum creatinine (4.9±2.6 vs. 2.7±1.8, p<0.001) and eGFR (18±14.4 vs. 43.4±37.1, p<0.001) between the ESKD and non-ESKD groups, respectively. The group of patients with ESKD had a higher number of globally sclerotic glomeruli (p=0.005), higher percentage of globally sclerotic glomeruli (p=0.013), and IFTA score (p=0.008) compared to non-ESKD patients group. However, no significant

Table 1: Baseline demographic characteristics, clinical features, and laboratory results of patients with crescentic glomerulonephritis

Parameters	All patients (n=91)
Age (years)	46.4±17.4
Gender (male/female)	54 (59)/37 (41)
Follow-up period (months)	17 (1-160)
Sedimentation (mm/hour)	56.3±31.8
Proteinuria (mg/day)	3690±2654
Hemoglobin (g/dL)	10.1±1.8
Hematocrit (%)	30.5±5.5
Neutrophil-to-lymphocyte ratio	4.9±4
C-reactive protein (mg/L)	30.6±37.4
Albumin (g/dL)	3±0.7
C-reactive protein-to-albumin ratio	11±14.7
Creatinine (mg/dL)	3.5±2.4
eGFR (CKD-EPI) (mL/min/1.73 m^2)	34±33
Total cholesterol (mg/dL)	201±61
LDL cholesterol (mg/dL)	127±50
HDL cholesterol (mg/dL)	40±11
Triglycerides (mg/dL)	174±95
SBP at the time of kidney biopsy (mmHg)	131±13
DBP at the time of kidney biopsy (mmHg)	80±13
Requirement for dialysis at presentation	21 (23)
Presence of macroscopic hematuria	9 (10)
Presence of microscopic hematuria	82 (90)
Presence of diabetes mellitus	10 (11)
Presence of hypertension	41 (45)
Presence of dyslipidemia	59 (65)
Presence of peripheral edema	30 (33)
PR3-ANCA positivity	16 (17.5)
MPO-ANCA positivity	15 (16.5)
Anti-GBM antibody positivity	6 (6.5)
Extrarenal organ involvement	
• Lung	20 (22)
• Ear-nose-throat	4 (4.4)
• Skin	7 (7.7)
• Hematologic	1 (1.1)
• Gastrointestinal	1 (1.1)
• Pericardial	2 (2.2)
Kidney biopsy indications	
• Rapidly progressive glomerulonephritis	74 (81)
• Nephrotic syndrome	9 (10)
• Nephritic syndrome	4 (4.5)
• Asymptomatic urinary abnormalities	4 (4.5)

Data are presented as number (%), mean ± standard deviation, median (minimum-maximum), or number only
eGFR: Estimated glomerular filtration rate, CKD-EPI: Chronic kidney disease epidemiology collaboration, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, PR3-ANCA: Proteinase 3-antineutrophil cytoplasmic antibody, MPO-ANCA: Myeloperoxidase-antineutrophil cytoplasmic antibody, GBM: Glomerular basement membrane

difference was observed in total crescentic glomeruli ratio between the non-ESKD group and the ESKD group (39.4±25.8 vs. 49.5±30.9, p=0.129, respectively). The characteristics and comparisons of the two groups are shown in Tables 3 and 4.

Treatment and Risk Factors Assessment

Of the 91 patients diagnosed with CGN, 76 (83.5%) and 58 (63.7%) received steroids and cyclophosphamide, respectively. Fifty-eight percent of the patients were additionally treated by azathioprine (n=36), mycophenolate mofetil (n=14), and rituximab (n=3). Fourteen patients received therapeutic plasma exchange at the time of diagnosis according to the underlying disease. The treatment protocols were given according to the Kidney Disease Improving Global Outcomes 2012 glomerulonephritis guidelines (17).

For the estimation of ESKD, on ROC analysis the optimal cut-off values for serum creatinine level was 3 mg/dL

Table 2: Histopathological characteristics of patients with crescentic glomerulonephritis

Parameters	All patients (n=91)
Total number of glomeruli	12 (2-38)
Total number of crescentic glomeruli	4 (1-31)
Number of globally sclerotic glomeruli	2 (0-27)
Cellular crescentic glomeruli ratio (%)	23.3±25.7
Total crescentic glomeruli ratio (%)	43±28
Global sclerotic glomeruli ratio (%)	25±24.7
Presence of fibrinoid necrosis	38 (41.8)
Presence of endocapillary proliferation	33 (36.3)
Presence of mesangial proliferation	45 (49.5)
Presence of arteriolar hyalinosis	8 (8.8)
Presence of arteriosclerosis	27 (29.7)
Presence of interstitial inflammation	89 (97.8)
Interstitial fibrosis and tubular atrophy score	
• 0	17 (18.6)
• <25%	44 (48.4)
• 25-50%	23 (25.3)
• >50%	7 (7.7)
Histopathologic diagnosis	
• Anti-GBM glomerulonephritis	7 (7.7)
• Lupus nephritis	13 (14.3)
• IgA nephropathy	26 (28.6)
• Infection-related glomerulonephritis	4 (4.4)
• Membranous glomerulonephritis	1 (1)
• ANCA-associated glomerulonephritis	40 (44)

Data are presented as number (%), mean ± standard deviation, median (minimum-maximum), or number only
GBM: Glomerular basement membrane, IgA: Immunoglobulin A, ANCA: Antineutrophil cytoplasmic antibody

Table 3: Comparison of the patients' characteristics between the non-ESKD and ESKD groups

Parameters	Non-ESKD (n=57, 63%)	ESKD (n=34, 37%)	p value
Age (years)	46.3±17	46.6±18.3	0.993
Gender			0.281
• Male	32 (56)	22 (65)	
• Female	25 (44)	12 (35)	
Follow-up period (months)	25 (1-160)	8.5 (1-60)	0.001
SBP (mmHg)	127±15	138±20	0.007
DBP (mmHg)	77±11	84±14	0.016
Proteinuria (mg/day)	3720±2848	3640±2334	0.863
Hemoglobin (g/dL)	10.4±1.6	9.6±2.1	0.018
Hematocrit (%)	31.6±4.9	28.5±5.9	0.012
Sedimentation (mm/hour)	54.6±30.3	59.3±34.5	0.653
Neutrophil-to-lymphocyte ratio	4.8±3.7	5.1±4.6	0.682
C-reactive protein (mg/L)	29.1±39.5	33.1±33.8	0.253
Albumin (g/dL)	3±0.7	3±0.6	0.883
C-reactive protein to albumin ratio	10.9±16.2	11.1±11.8	0.267
Creatinine (mg/dL)	2.7±1.8	4.9±2.6	<0.001
GFR (CKD-EPI) (mL/min/1.73. m^2)	43.4±37.1	18±14.4	<0.001
Total cholesterol (mg/dL)	205±64	194±55	0.462
LDL cholesterol (mg/dL)	129±53	123±43	0.674
HDL cholesterol (mg/dL)	42±12	36±8	0.008
Triglycerides (mg/dL)	170±99	181±90	0.523
Need for dialysis at presentation			<0.001
• Yes	4 (7)	17 (50)	
• No	53 (93)	17 (50)	
Presence of macroscopic hematuria	4 (7)	5 (15)	0.189
Presence of microscopic hematuria	53 (93)	29 (85)	0.281
Presence of diabetes mellitus	5 (8.7)	5 (14.7)	0.281
Presence of hypertension	20 (35)	21 (61.7)	0.007
Presence of dyslipidemia	36 (63)	23 (67.6)	0.318
Presence of peripheral edema	16 (28)	14 (41)	0.161
ANCA positivity			0.168
• PR3-ANCA	8 (14)	8 (23.5)	
• MPO-ANCA	11 (19.2)	4 (11.7)	
Patient survival			0.1
• Alive	52 (91)	27 (80)	
• Died	5 (9)	7 (20)	

Data are presented as number (%), mean ± standard deviation, median (minimum-maximum), or number only
ESKD: End-stage kidney disease, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, eGFR: Estimated glomerular filtration rate, CKD-EPI: Chronic kidney disease epidemiology collaboration, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, ANCA: Antineutrophil cytoplasmic antibody, PR3-ANCA: Proteinase 3-antineutrophil cytoplasmic antibody, MPO-ANCA: Myeloperoxidase-antineutrophil cytoplasmic antibody

[area under the curve (AUC): 0.76, 95% confidence interval (CI): 0.671-0.866, p<0.001] and for global sclerotic glomeruli ratio was 24% (AUC: 0.65, 95% CI: 0.536-0.770, p=0.015). The ROC curves of serum creatinine level and global sclerotic glomeruli ratio are shown in Figure 1. The Cox regression analysis was used to identify risk factors that predict ESKD. The variables for which p<0.20 was found by univariate analysis were included in the multivariate regression analysis. According to the univariate Cox regression analysis results, gender, global sclerotic glomeruli ratio, total crescentic glomeruli ratio, baseline serum creatinine level, IFTA score and need for dialysis on admission were taken as a candidate variable in multivariate analysis. On multivariate analysis, the requirement for dialysis [hazard ratio (HR): 2.4, 95% CI: 1.06-5.40, p=0.034], the serum creatinine level >3 mg/dL (HR: 2.92, 95% CI: 1.05-8.10, p=0.040), and IFTA score >25% (HR: 2.85, 95% CI: 1.31-6.20, p=0.008) were independent risk factors for the development of ESKD. Risk factors for the development of ESKD are shown in Table 5.

Table 4: Comparison of the patients' histopathological findings between the non-ESKD and ESKD groups

Parameters	Non-ESKD (n=57, 62.7%)	ESKD (n=34, 37.3%)	p value
Total number of glomeruli	12 (2-37)	13 (3-18)	0.340
Total number of crescentic glomeruli	4 (1-24)	5 (1-31)	0.082
Number of globally sclerotic glomeruli	1 (0-10)	4 (0-27)	0.005
Cellular crescentic glomeruli ratio (%)	23.5±24.9	23±27	0.670
Total crescentic glomeruli ratio (%)	39.4±25.8	49.5±30.9	0.129
Globally sclerotic glomeruli ratio (%)	19.9±21.4	33.8±27.5	0.013
Presence of fibrinoid necrosis	25 (43.9)	13 (38.2)	0.381
Presence of endocapillary proliferation	23 (40.4)	10 (29.4)	0.205
Presence of mesangial proliferation	29 (50.9)	16 (47.1)	0.446
Presence of arteriolar hyalinosis	3 (5.3)	5 (14.7)	0.125
Presence of arteriosclerosis	16 (28.1)	11 (32.4)	0.420
Presence of interstitial inflammation	55 (96.5)	34 (100)	0.912
Interstitial fibrosis and tubular atrophy score			0.008
• <25%	44 (77.2)	17 (50)	
• >25%	13 (22.8)	17 (50)	

Data are presented as number (%), mean ± standard deviation, median (minimum-maximum), or number only
ESKD: End-stage kidney disease

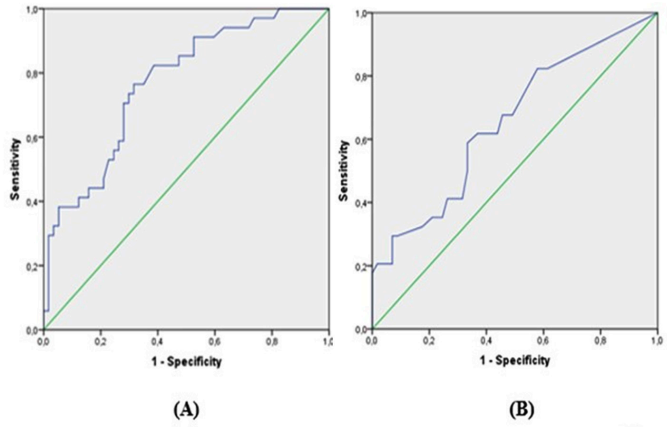

Figure 1: The ROC curve of serum creatinine level and global sclerotic glomeruli ratio for predicting kidney outcome. A) The serum creatinine level of 3 mg/dL was determined to be a cut-off value with a sensitivity of 76% and a specificity of 68%, and the AUC was 0.76. B) The global sclerotic glomeruli ratio of 24% was determined to be a cut-off value with a sensitivity of 62% and a specificity of 63%, and the AUC was 0.65.

Discussion

In the present study, the results showed that the ESKD group had a high prevalence of hypertension, high levels of SBP and DBP, more advanced kidney failure, and high rate of need for dialysis therapy. Moreover, patients in the ESKD group also had a higher global sclerotic glomeruli ratio, IFTA score, and lower levels of hemoglobin and hematocrit compared with non-ESKD group. In multivariate analysis, we found that the serum creatinine level above 3 mg/dL, need for dialysis treatment, and presence of more than 25% IFTA at the time of diagnosis in CGN patients were independent risk factors for ESKD.

RPGN is a clinical syndrome characterized by a rapid decline in kidney function that typically accompanies CGN and often causes ESKD. Quick action is important here, timely and accurate clinical and pathological diagnosis are essential. Rapid initiation of appropriate therapy is crucial in efforts to reverse irreversible organ damage (18).

As kidney failure advances, especially the presence of need for dialysis therapy at presentation determines the prognosis with regard to mortality and kidney survival. However, it is unclear which cut-off value of serum creatinine level could be indicative of poor kidney outcome (3).

Histologically, a low percentage of normal glomeruli and large extent of IFTA, and extent of interstitial infiltrate are associated with poor kidney outcomes (9,10,19). In a recent study, researchers demonstrated that the specific histopathologic findings, such as histopathologic classification, the severity of arteriosclerosis, and tertiary lymphoid organ formation provide additional information in predicting kidney outcomes among CGN patients.

Table 5: Cox regression analysis: risk factors associated with end stage kidney disease in patients with crescentic glomerulonephritis								
Parameters		Univariate				Multivariate		
	HR	95% CI		p value	HR	95% CI		p value
		Low	Up			Low	Up	
Gender (male)	1.62	0.80	3.28	0.181	-	-	-	-
Globally sclerotic glomeruli ratio (>24%)	2.76	1.37	5.55	0.004	-	-	-	-
Need for dialysis at presentation	5.18	2.59	10.36	<0.001	2.40	1.06	5.40	0.034
Creatinine (>3 mg/dL)	6.37	2.80	14.51	<0.001	2.92	1.05	8.10	0.040
Total crescentic glomeruli ratio	1.01	0.99	1.02	0.190	-	-	-	-
Interstitial fibrosis and tubular atrophy score (>25%)	4.30	2.03	9.11	<0.001	2.85	1.31	6.20	0.008
HR: Hazard ratio, CI: Confidence interval								

Also, clinical parameters such as age and kidney function at the time of diagnosis were identified as independent predictors of kidney outcomes (20). In a new study reported from the Mayo Clinic, investigators defined a chronicity score on kidney biopsy including chronic changes such as glomerulosclerosis, interstitial fibrosis, tubular atrophy and arteriosclerosis. The chronicity score grades were correlated with the severity of kidney function impairment at presentation. Higher degrees of involvement of each component was correlated with lower eGFR at diagnosis and increased risk of kidney disease progression in patients with ANCA-associated glomerulonephritis (21). The findings of the present study were similar to the findings of the above mentioned studies. We observed that 37% of the patients resulted in ESKD during a median follow-up of 17 months. The degree of decline in kidney function at presentation, need for dialysis therapy, and the presence of IFTA on kidney biopsy were independent prognostic predictors of kidney outcomes in our study.

Recently, the Turkish Society of Nephrology Glomerular Diseases Working Group has published an article regarding the epidemiologic data of patients with RPGN in Türkiye (22). This study's results are consistent with our study results. However, the present study is seperated from this study by determining the predictor factors of ESKD in CGN patients. Also, our data were reflected from a tertiary referral center. Thus, we think that our study report can provide detailed information about patient characteristics and risk factors affecting kidney prognosis in CGN patient population from our country.

The kidney prognosis of CGN patients depends on many factors, including the underlying cause, serum creatinine level at presentation, percentage of glomerular involvement, treatment delay, and several specific histopathologic findings. The histopathologic severity, activity, and chronicity of glomerular and tubulointerstitial compartments can predict the prognosis. Although CGN is defined commonly as the presence of >50% crescent in a kidney biopsy, there is no consensus about the term of CGN among pathologists. Also depending on the clinical condition, there may be major diagnostic and clinical significance in the finding of one fresh crescent formation in the kidney biopsy specimen (2). In this study, our biopsy specimens had various percentages of total crescentic glomeruli, ranging between 10-100%. The mean total crescentic glomeruli ratio was 43% (celluler crescent 23%, fibrocellular crescent 14.5%, and fibrous crescent 5.5%). Aproximately one-third of the patients had crescent ≥50%. When we examined the patients based on different crescent percentages, the group of patients with ≥50% crescents had more severe renal insufficiency at presentation and more frequent dialysis requirement. However, total crescentic glomeruli ratio was not a prognostic factor for ESKD in our study. This may be related to relatively small sample size, short duration of follow-up period in our center.

Patients with advanced chronic histopathological findings must be balanced against the possibility of immunosuppressive-related adverse effects. There's no established simple prognostic marker for accurately predicting kidney outcome. Still, the best prognostic marker for all CGN patients is the severity of kidney function impairment at the time of diagnosis (3,18). For this reason, early diagnosis and treatment, increasing awareness of the disease among clinicians and multidisciplinary management of the complex disease are very important for preventing irreversible organ damage and increasing kidney survival in CGN patients.

Study Limitations

The present study had several limitations. This was a single-center retrospective study including a relatively small number of patients with various glomerular disease entities. Therefore, the data of the present study could not be analyzed in a standardized fashion. A large-scale, longer follow-up and multicentre study based on national data are needed to evaluate risk factors for the development of ESKD.

Conclusions

This study demonstrated that the kidney function at the time of diagnosis, need for dialysis therapy, and the presence of IFTA

on kidney biopsy are predictive factors for kidney outcomes in CGN patients. Treatment plans must be individualized according to chronic changes on kidney biopsy and in patients whose kidney function is unlikely to recover. Further studies are needed to define which risk factors are best suited for CGN patients.

Ethics

Ethics Committee Approval: This study protocol was approved by the Ankara University Faculty of Medicine Ethics Committee for Clinical Studies and was in adherence with the Declaration of Helsinki (approval no.: 07-440-18, date: 16.04.2018).

Informed Consent: Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Authorship Contributions

Surgical and Medical Practices: Ş.E., R.E.S., G.K.Ş., F.K., S.K., Concept: Ş.E., Ş.Ş., Design: Ş.E., Ş.Ş., Data Collection and/or Processing: Ş.E., R.E.S., G.K.Ş., Analysis and/or Interpretation: Ş.E., F.K., S.K., S.Ku., K.K., G.N., K.A., Ş.Ert., Ş.Ş., Literature Search: Ş.E., R.E.S., G.K.Ş., Writing: Ş.E.

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