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PREDICTORS OF RENAL OUTCOME IN ANCA-ASSOCIATED GLOMERULONEPHRITIS

PREDIKTORI BUBREŽNOG ISHODA KOD ANCA-UDRUŽENIH GLOMERULONEFRITISA

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Abstract

**Background / Aim.** Primary ANCA-associated vasculitis are chronic multisystemic autoimmune diseases in which they are counted microscopic polyangitis (MPA), granulomatosis with polyangitis (WG), eosinophilic granulomatosis with polyangitis (EPGA; CSS), and also a localized forms of illness. In our research, we studied clinical and serological parameters in patients, in order to find out which of them would be the best predictor of renal outcome in ANCA-associated vasculitis. **Methods.** Data from 42 patients with diagnose of MPA (9), WG (17), EPGA (0), CSS (0), and also idiopathic raphidoprogressive glomerulonephritis without immune deposits (renal-limited vasculitis) (16) were analyzed. Cockroft formula was used for calculating the glomerular filtration in the moment of presenting the illness, and also after five year follow-up period. Other factors that were analyzed are: gender, age, type of ANCA antibodies, type of infections, stage of chronic kidney disease, need for hemodialysis and mortality. **Results.** Of a total of 42 patients, 17 (40.48%) were male. The average age of the patients at the time of diagnosis was 57.8 (± 10.44) years. 17 patients (40.48%) had a diagnosis of WG, 9 (21.43%) MPA, and 16 iRPGN (38.09%). The presence of positive anti-PR3 antibodies was confirmed in 18 patients, and anti-MPO antibodies in 17 patients. 3 patients had both subtypes of ANCA antibodies (anti-PR3 and anti-MPO). Initially, 12 patients required hemodialysis treatment. 29 patients had a complete and 13 patients had partial remission. Out of the total number of patients, 8 patients (19.04%) developed the terminal renal failure stage, and ended up on a chronic dialysis program. During a five-year follow-up period, 12 patients (28.57%) resulted in death. The age of the patient proved to be statistically significant predictor of GFR at the moment of presentation of the disease ( p=0.011). GFR t = 0 was statistically significant ( p= 0.000) for the evaluation of kidney function outcomes in ANCA-associated glomerulonephritis. **Conclusion.** In conclusion of our research, we can say that kidney function in the moment of illness presentation is the most important significant factor for predicting renal outcome in ANCA-associated vasculitis, and also the mortality in these patients.

**Key words:** ANCA, prognosis, renal outcome.
Apstrakt

Uvod / Cilj. Primarni ANCA-udruženi vaskulitisi predstavljaju hronično multisistemsko autoimuno oboljenje u koje se ubrajaju mikroskopski poliangitis (MPA), granulomatoza sa poliangitisom (WG), eozionofilna granulomatoza sa poliangitisom (EPGA; CSS), kao i lokalizovane forme bolesti. U našem ispitivanju, koristili smo kliničke i serološke parametre kod bolesnika, kako bismo pronašli koji od njih bi bili najbolji prediktori bubrežnog ishoda kod ANCA-udruženih glomerulonefritisa. Metode. Analizirani su podaci 42 bolesnika sa dijagnozom MPA (9), WG (17), eozionofilna granulomatoza sa poliangitism (EPGA; CSS) (0), kao i idiopatski rapido-progresivni glomerulonefritis bez imunih depozita (renal-limited vasculitis) (16). Cockcroft formula je upotrebljena za izračunavanje glomerulske filtracije u momentu prezentacije bolesti, i nakon petogodišnjeg praćenja bolesnika. Ostali faktori koji su analiziranu su: pol, starost, tip ANCA antitela, tip infekcija, stepen HBI, potreba za hemodijalizom i mortalitet. Rezultati. Od ukupno 42 pacijenta, 17 (40,48%) su bili muškog pola. Prosečna starost pacijenata u vreme postavljanja dijagnoze bila je 57,8 (± 10,44) godina. Prisustvo pozitivnih anti-PR3 antitela potvrđeno je kod 18 pacijenata, a anti-MPO antitela kod 17 pacijenata. Pozitivnost anti-PR3 i anti-MPO antitela dokazana je kod 3 pacijenata. Inicijalno, hemodijalizni tretman je sproveden kod 12 pacijenata. Nakon sprovedene terapije kod 29 pacijenata je postignuta potpuna a kod 13 pacijenata delimična remisija. Od ukupnog broja pacijenata, 8 (19,04%) je razvilo terminalni stadijum slabosti bubrega i nastavilo lečenje hroničnim hemodijalizama. Tokom perioda praćenja od pet godina, 12 pacijenata (28,57%) je umrlo. Starost bolesnika se pokazala statistički značajnim prediktorom GFR-a u momentu prezentacije bolesti ( p=0.011). GFR t=0 pokazao se statistički značajnim ( p= 0.000) za procenu ishoda bubrežne funkcije kod ANCA-udruženih glomerulonefritisa. Zaključak. Kao zaključak našeg ispitivanja, možemo reći da bubrežna funkcija u momentu prezentovanja bolesti, određena putem GFR t=0, predstavlja jedini značajni faktor za procenu ishoda bubrežne funkcije kod ANCA-udruženih glomerulonefritisa, kao i mortaliteta ovih bolesnika.

Ključne reči: ANCA, prognoza, bubrežni ishod.
Introduction

Primary types of vasculitis that are associated with anti-neutrophil cytoplasm antibody (ANCA-associated vasculitis; AAV) are chronic multisystemic autoimmune diseases in which they are counted microscopic polyangitis (MPA), granulomatosis with polyangiitis (WG), eosinophilic granulomatosis with polyangiitis (EPGA; CSS), and also a localized forms of illness. After receiving the corticosteroid and immunosuppressive therapy, most of the patients experience early remission, but patients with ANCA-associated vasculitis continue to be at increased fatal risk compared with a healthy population.

Kidney affection is one of the most common manifestation of vasculitis and it has a great impact on the outcome of the disease. Renal vasculitis is the most common severe manifestation of ANCA-associated vasculitis (AAV) and it is typically presented with rapidly progressive glomerulonephritis (GN). During the diagnostic phase of AAV, dialysis is often needed, but however renal recovery and withdrawal from dialysis after the treatment is possible, in more than 50% patients. Renal impairment at prognosis also is a predictor of poor renal outcome and also of poor patient survival.

Treatment of AAV may also cause significant morbidity, and patients with impaired renal function may be particulary prone to treatment-emergent adverse events. Medication based on cyclophosphamide (CYC) and corticosteroids (CS), which have been used since the 1970s, changed the prognosis of AAV from lethal to a chronic relapsing disease. Around a half of the patients have a relaps within five years after diagnosis.

Mortality of the patients with ANCA-associated vasculitis is high 10-15% within the first year following treatment initiation. These patients have 2.7-fold increase in mortality compared with the general population. Some of the studies have shown that the mortality of the patients with renal involvement depends on factors such as: older age, side effects of the therapy, lung haemorrhage, high disease activity score based on the Birmingham Vasculitis Activity Score (BVAS) etc.

In order to control the inflammation, patients are treated with immunosuppressive and/or cytostatic therapy.

In our study, we used clinical and serological parameters in 42 patients, in order to find out which of them would be the best predictor of renal outcome in ANCA-associated vasculitis.
Methods

42 patients, with diagnose of WG, MPA, CSS, idiopathic rapidoprogressive glomerulonephritis (iRPGN) were enroled in this study. Disease diagnose was based on the Chapel Hill Consensus Conference criteria for ANCA-associated vasculitis. Inclusion criteria were: (1) positive anti-myeloperoxidase-antineutrophilic antibodies (anti-MPO-ANCA), or anti-proteinase 3- antineutrophilic antibodies (anti-PR3-ANCA); (2) kidney damage; rapid increase of serum creatinine. Glomerular filtration rate (GFR) was calculated by Cockroft formula and it was used as a marker of kidney function. GFR was determined in the moment of kidney biopsy (t=0), and after a five year follow-up period. In order to do analysis less complicated, CSS and iRPGN were marked as renal-limited form of vasculitis, because, separated, those date would be statistically insignificant. Patients with secondary vasculitis, including lupus nephritis, were excludes from the study. Induction terapeutic aproach was consistent from the following: 1. methilprednisolone and cyclophosphamide, 2. methilprednisolone, cyclophosphamide and terapeutic plasma exchange, 3. methilprednisolone, 4. cyclophosphamide. After achieving remission, the therapy was: 1. azathioprin per oral 2mg/kg/24h , 2. mycophenolat mofetil 2-3g/24h, 3. combination of corticosteroid therapy and azathyoprin, in patients whose condition went worse after stopping corticosteroids. Statistical data processing was performed in IBM SPSS Statistics v.23. Categorical variables are represented by absolute and relative frequencies. The central tendency of the continuous variables is represented by the arithmetic mean, the deviation with the standard deviation, the minimum and the maximum. Multivariate linear regression models have been studied by the predictors of the renal function of the patient at the time of presentation of the disease and after the follow-up of the period. The stability of the 95% predictor confidence interval was confirmed by the bootstrap resampling method with 1000 samples and the Mersenne Twister random number generator. (bootstrapping confirms that predictive models remain the same on a larger sample, that is, not to get different results when the sample would be larger).

Results

Of a total of 42 patients, 17 (40.48%) were male. The average age of the patients at the time of diagnosis was 57.8 (± 10.44) years. 17 patients (40.48%) had a diagnosis of GW, 9 (21.43%) MPA, and 16 iRPGN (38.09%). None of the patients had CSS. The presence of
positive anti-PR3 antibodies was confirmed in 18 patients, and anti-MPO antibodies in 17 patients. 3 patients had both subtypes of ANCA antibodies (anti-PR3 and anti-MPO). At the time of diagnosis, the mean value of the glomerular filtration volume (eGFR) was 52.71 ml / min / 1.73 m² (eGFR values ranged from 4 to 156 ml / min /1.73 m²). Nine patients had preserved kidney function, five of them had stage 1 of CKD, five had stage 2 CKD, five had stage 3 CKD, six had stage 4 of CKD, and twelve stage 5 of CKD. In 19 patients, the presence of pulmonary lesions was established. Therapeutic protocols involved the following options: 25 patients received a combination of methylprednisolone and cyclophosphamide (14 patients with WG; 7 patients with MPA; 4 patients with iRPGN), 13 patients metilprednisolone, cyclophosphamide and plasma therapeutic modification (4 patients with WG; 8 patients with MPA; 1 patient with iRPGN), 3 patients metilprednisolone as a monotherapy because of the neutropenia (2 patients with WG, 1 patient with iRPGN), 1 patient cyclophosphamide due to unregulated diabetes (patient with MPA). Initial doses of corticosteroid therapy was 1mg/kg intravenous, and for cyclophosphamide 500-750 mg/m² (applied monthly). Plasma exchange therapy was applied in 13 patients, who had severe alveolar haemorrhage and ESRD in the moment of disease presentation. The number of plasma therapeutic modification was: 5 procedures in patients with WG, 5 procedures in patients with MPA, 3 procedures in patient with iRPGN. Initially, 12 patients required haemodialysis treatment (2 patients with iRPGN, 6 patients MPA, 4 patients with WG). 29 patients had a complete and 13 patients had partial remission. Table 1 presents the clinical characteristics of patients in the moment of disease presentation (Table 1). The most common cause of hospitalization of patients with ANCA vasculitis were infections: urinary tract infections (in 11 patients), then lower respiratory tract (in 6 patients), and upper respiratory tract (ear, throat and nose) (in 6 patients). After five-year follow up period, 14 patients did not have kidney weakness, and in other patients the most frequent was the grade 2 renal failure. Out of the total number of patients, 8 patients (19.04%) developed the terminal renal failure stage, and ended up on a chronic dialysis program (2 patients with iRPGN, 4 patients with MPA, 2 patients with GW). Six of these patients were initially on haemodialysis, and two of them had partially remission after initial treatment and were corticosteroid dependent. During a five-year follow-up period, 12 patients (28.57%) resulted in death (1 patient with iRPGN, 7 patients with MPA, 4 patients with GW). Seven of these patients were initially on haemodialysis, and cause of death was
alveolar hemmorhage in 4 patients, and severe infections in 8 patients. Table 2 presents the clinical characteristics of patients after five-year follow up period (Table 2).

Based on the results of the general significance test ($F(1.40) = 7.155$, $p = 0.011$), one can conclude that the predictive GFR model in $t = 0$ is statistically significant. According to $R^2 = 0.152$ the model explains 15.2% variation of the dependent variable.

The age of the patient proved to be statistically significant predictor of GFR at the moment of presentation of the disease. Estimated glomerular filtration decreases with the age of patients with a factor of 0.390 (Table 3).

Based on the results of the general significance test ($F(4.37) = 16.633$, $p = 0.000$), it is concluded that the predictive GFR model in $t = 5$ is statistically significant. The corrected determination coefficient shows that the model explains 60.4% of variation of the dependent variable.

Of all potential renal outcome predictors, only GFR $t = 0$ was statistically significant, which was directly proportional to the factor 0.818 (Table 4).

**Discussion**

This retrospective study was done with a purpose to identify the best predictors of renal outcome in AAV. Renal dysfunction is known risk factor for mortality in patients with AAV, and for that reason, the accent on providing the better outcome should be focused on the treatment of renal vasculitis. Better understanding of the factors that are associated with the prognosis of AAV can help to choose the right therapeutic approach in patient with this diagnose. Despite the significant kidney damage, in our study 34 patients were not dialysis-dependent. End-stage kidney disease was developed in 8 patients, and 12 (28.57%) patients had lethal outcome due to complications of the disease itself, or of the therapy. Our results are similar to the multicentric clinical research of the Walsch et al, and prospective multicentric clinical study de Lind van Wijngaarden et al (21%) and Titeca-Beauport et al (36.61%) In our research, 13 patients had additional plasma exchange therapy. There was no statistically significant impact of the plasma exchange therapy on the outcome of the patients. These results are different from the MEPEX study, in which the patients who received plasma exchange therapy had better outcome of renal function. The data on antibody subtypes and prognosis of renal function are different. Recent studies have shown
that MPO ANCA-positive patients have significantly more expressed chronic changes in kidney biopsies than patients with PR3 ANCA. Other histological research did not prove the difference between antiPR3 and antiMPO antibodies. In our study, we have noticed that the subtypes of ANCA antibodies affect the prognosis. Average GFR t=0 was significantly higher in patients with antiPR3 antibodies than in patients with antiMPO antibodies. The difference was not verified in patients after the five-year follow-up period (GFR t=5). 21 patients (50%) had renal-limited form of disease, and in 19 patients (70.37%) lung damage was present. Infection are one of the main problems during the treatment of AAV, and also are the main cause of death in immunosuppressed patients. Unlike the study of Kronbichler et al., in our work, the most frequent were urinary tract infections (26.19%). Also, hospitalization of patients with ANCA vasculitis due to infections was less common than in the published studies so far, where cumulative incidence at 1, 2 and 5 years of any infection was 51, 58 and 65%. As a conclusion of our study, we can say that the renal function at the moment of presentation of the disease, determined by GFR t = 0, is the most important independent factor for assessing the outcome of renal function in ANCA-associated glomerulonephritis, as well as the mortality of these patients.

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Table 1. Clinical characteristics of patients in the moment of disease presentation

|                          | f   | %    |
|--------------------------|-----|------|
| **Gender**               |     |      |
| Male                     | 17  | 40.48|
| Female                   | 25  | 59.50|
| **Age**                  |     |      |
| Min                      | 30  |      |
| Max                      | 83  |      |
| M                        | 57.786 |    |
| SD                       | 10.44 |   |
| **ANCA subtype**         |     |      |
| antiMPO                  | 17  | 41   |
| antiPR3                  | 18  | 43   |
| antiPR3 + antiMPO        | 3   | 7    |
| undifferentiated         | 4   | 10   |
| iRPGN                    | 16  | 38.09|
| **Diagnosis**            |     |      |
| MPA                      | 9   | 21.43|
| GPA                      | 17  | 40.48|
| Skin                     | 5   | 18.52|
| Lung                     | 19  | 70.37|
| **Affection of other organs** |     |      |
| ORL                      | 3   | 11.11|
| In total                 | 27  | 100  |
| CYP                      | 1   | 2.40 |
| CS                       | 3   | 9.60 |
| **Induction therapy**    |     |      |
| CS+CYP                   | 25  | 59.50|
| CS+CYP+PF                | 13  | 31   |
| Min                      |     |      |
| Max                      |     |      |
| M                        |     |      |
| SD                       |     |      |
| **GFR t=0**              |     |      |
| Preserved                | 9   | 21.42|
| CKD grade 1              | 5   | 11.90|
| CKD grade 2              | 5   | 11.90|
| CKD grade 3              | 5   | 11.90|
| CKD grade 4              | 6   | 14.28|
| CKD grade 5              | 12  | 28.57|
|                | iRPGN | 2 |
|----------------|-------|---|
|                | MPA   | 6 |
|                | GPA   | 3 |

| HD t=0         |       |   |
|----------------|-------|---|
|                |       |   |

| Table 2. Clinical characteristics of patients after five-year follow up period |
|-----------------------------------------------------------------------------|
|                                                                             |
| **Infections**                                                              |
|                                                                             |
| Encephalitis                   | 1     | 4.76 |
| RTI                           | 6     | 28.57 |
| UTI                           | 11    | 52.38 |
| Mediastinitis                 | 1     | 4.76 |
| ORL                           | 6     | 28.57 |
| In total                      | 21    | 100  |
| **GFR t=5**                   |       |     |
|                                                                             |
| Min                          | M     | SD  |
|                                                                             |
| 1x                            | 4     | 58.21 37.54 |
| 8                             |       |     |
| Preserved                     | 14    | 34.10 |
| CKD grade 1                   | 1     | 2.40  |
| CKD grade 2                   | 11    | 26.80 |
| CKD grade 3                   | 7     | 17.10 |
| CKD grade 4                   | 1     | 2.40  |
| CKD grade 5                   | 8     | 17.10 |
| **Kidney function after five year follow up period**                        |
|                                                                             |
| No                            | 34    | 82.90 |
| Yes                           | 8     | 17.10 |
| **Mortality**                 |       |     |
| No                            | 30    | 71.40 |
| Yes                           | 12    | 28.57 |
### Table 3. Predictive model for GFR t = 0

| Predictors | Coefficient | t  | p     | 95% BCI        |
|------------|-------------|----|-------|----------------|
| Constant   | 4.143       | 0.000* | 72.039 240.803 |
| Age        | -0.390      | 0.011* | -3.147 -0.372  |

### Table 4. Predictive model for GFR t=5

| Predictors | β   | t    | p     | 95% BCI        |
|------------|-----|------|-------|----------------|
| Constant   | 0.532 | 0.598 | -23.131 36.839 |
| GFR t=0    | 0.818 | 7.682 | 0.000* | 0.509 0.957     |
| Therapy    | 0.073 | 0.672 | 0.506 | -12.143 22.556 |
| Infections | 0.106 | 1.051 | 0.300 | -1.798 6.520   |
| ANCA subtype | 0.026 | 0.228 | 0.821 | -7.036 7.789   |

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