ORIGINAL ARTICLE

UDC: 616.61-002-036
DOI: https://doi.org/10.2298/VSP190903135L

Predictors of renal outcome in ANCA-associated glomerulonephritis

Prediktori bubrežnog ishoda kod ANCA-udruženih glomerulonefritisa

Bojana Ljubičić*, Tijana Azaševac†, Milica Popović†‡, Siniša Živković†, Dušan Božić†‡, Dejan Ćelić†‡

Clinical Centre of Vojvodina, Emergency Centre, *Department of Emergency Internal Medicine, †Clinic for Nephrology and Clinical Immunology, Novi Sad, Serbia; ‡University of Novi Sad, Faculty of Medicine, Department of Internal Medicine, Novi Sad, Serbia

Abstract

Background/Aim. Primary anti-neutrophil cytoplasmatic antibody (ANCA)-associated vasculitis are chronic multisystemic autoimmune diseases which include microscopic polyangitis (MPA), granulomatosis with polyangitis (WG), eosinophilic granulomatosis with polyangitis (EPGA; churg-strauss syndrome – 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 rapidly progressive glomerulonephritis (ROEB) 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 heamodialysis 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. Seventeen patients (40.48%) had a diagnosis of WG, 9 (21.43%) MPA, and 16 (38.09%) iRPGN. The presence of positive anti-proteinase (anti-PR3) antibodies was confirmed in 18 patients, and anti-MPO antibodies in 17 patients. Three patients had both subtypes of ANCA antibodies (anti-PR3 and anti-MPO). Initially, 12 patients required heamodialysis treatment. Twenty nine 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 glomerular filtration rate (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.** Kidney function in the moment of illness presentation, determined by GFR t = 0, is the most important significant factor for predicting renal outcome in ANCA-associated vasculitis, and also the mortality in these patients.

Key words:
glomerulonephritis; antibodies, antineutrophil cytoplasmic; glomerular filtration rate; mortality.

Apstrakt

Uvod/Cilj. Primarni anti-neutrofilna citoplazmatska antitela (ANCA)-udruženi vaskulitisi predstavljaju hronično multisistemsko autoimunsko oboljenje u koje se ubrajaju mikroskopski poliangiitis (MPA), granulomatoza sa poliangiitisom (WG), eozionofilna granulomatoza sa poliangiitsom (EPGA; Churg-Stranss sindrom – 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 poliangiitsom (EPGA; CSS) (0), kao i idiopatski rapido-progresivni glomerulonefritis bez imunskih depozita (16). Cockcroft formula je upotrebljena za izračunavanje glomerulske filtracije u momentu prezentacije bolesti i nakon petogodišnjeg praćenja bolesnika. Ostali faktori koji su analizirani bili su: pol, starost, tip ANCA antitela, tip infekcija, stepen hronične bubrežne insuficijencije (HBI), potreba za hemodijalizom i mortalitet. **Rezultati.** Od ukupno 42 bolesnika, 17 (40,48%) su bili muškog pola. Prosečna starost bolesnika u vreme postavljanja dijagnoze bila je 57,8 ± 10,44 godina. Prisustvo pozitivnih anti-proteinaze 3 (anti-PR3) antitela potvrđeno je kod 18 bolesnika, a anti-MPO antitela kod 17 bolesnika. Pozitivnost anti-PR3 i anti-MPO antitela dokazana je kod tri bolesnika. Inicijalno, hemodijalizni tretman je

Correspondence to: Ljubičić Bojana, Clinical Centre of Vojvodina, Emergency Centre, Department of Emergency Internal Medicine, Hajduk Veljkova 1-11, 21 000 Novi Sad, Serbia. E-mail: bojanaljubicic21@gmail.com

sproveden kod 12 bolesnika. Nakon sprovedene terapije kod 29 bolesnika postignuta je potpuna, a kod 13 bolesnika delimična remisija. Od ukupnog broja bolesnika, osam (19,04%) je razvilo terminalni stadijum slabosti bubrega i nastavilo lečenje hroničnim hemodijalizama. Tokom perioda praćenja od pet godina, 12 bolesnika (28,57%) je umrlo. Starost bolesnika bila je statistički značajan predictor brzine glomerularne filtracije (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.** 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 kod ovih bolesnika.

Ključne reči:
glomerulonefritis; antitela, antineutrofilna, citoplazmatska; glomerulska filtracija; mortalitet.

Introduction

Primary types of vasculitis that are associated with antineutrophil cytoplasm antibody (ANCA-associated vasculitis; AAV) are chronic multisystemic autoimmune diseases which include microscopic polyangiitis (MPA), granulomatosis with polyangiitis (WG), eosinophilic granulomatosis with polyangiitis (EPGA; Churg-Strauss syndrome – 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 [1].

Kidney affection is one of the most common manifestation of vasculitis and it has a great impact on the outcome of the disease [2, 3]. 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, however renal recovery and withdrawal from dialysis after the treatment is possible, in more than 50% patients [4]. Renal impairment as prognosis is also a predictor of poor renal outcome [5–8] and also of poor patient survival [1, 9].

Treatment of AAV may also cause significant morbidity, and patients with impaired renal function may be particularly prone to treatment-emergent adverse events [4]. Medication based on cyclophosphamide (CYC) and corticosteroids (CS), which have been used since the 1970s [10], changed the prognosis of AAV from lethal to a chronic relapsing disease. Around a half of the patients have a relapse within five years after diagnosis [11, 12].

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 [13–18]. 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

Forty two 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 ANC-associated vasculitis [10]. Inclusion criteria were: positive anti-myeloperioxidase-antineutrophilic antibodies (anti-MPO-ANCA) or anti-proteinase 3- antineutrophilic antibodies (anti-PR3-ANCA); 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 [11]. GFR was determined in the moment of kidney biopsy (t = 0), and after a five year follow-up period. In order to do analysis in a less complicated manner, CSS and iRPGN were marked as renal-limited form of vasculitis, because separated, those data would be statistically insignificant. Patients with secondary vasculitis, including lupus nephritis, were excluded from the study. Induction therapeutic approach was consistent as follows: methylprednisolone and cyclophosphamide; methylprednisolone, cyclophosphamide and therapeutic plasma exchange; methylprednisolone; cyclophosphamide. After achieving remission, the therapy was: azathioprin *peroral* 2 mg/kg/24 h; mycophenolat mofetil 2–3 g/24 h; 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 model were studied by the predictors of the renal function of the patient at the time of presentation of the disease and after the follow-up period. The stability of the 95% predictor confidence interval was confirmed by the bootstrap resampling method with 1,000 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

Characteristics of patients included in the study are given in Table 1. 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. Seventeen 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. Three 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 m^2 (eGFR values ranged from 4 to 156 mL/min /1.73 m^2). Nine patients had preserved kidney function, five of them had stage 1 of chronic kidney disease (CKD), five had stage 2 of CKD, five had stage 3 of 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 GW; 7 patients with MPA; 4 patients with iRPGN), 13 patients methylprednisolone, cyclophosphamide and plasma therapeutic modification (4 patients with WG; 8 patients with MPA; 1 patient with iRPGN), 3 patients methylprednisolone 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/m^2 (applied monthly). Plasma exchange therapy was applied in 13 patients, who had severe alveolar heamorrhage and end-stage renal disease (ESRD) in the moment of disease presentation. The number of plasma therapeutic modification

Table 1

Clinical characteristics of patients at the moment of the disease presentation (t = 0)

Parameters	Values
Gender, n (%)	
male	17 (40.48)
female	25 (59.50)
Age (years), min-max; mean ± SD	30-83; 57.77 ± 10.44
Anti-neutrophil cytoplasmatic antibody (ANCA) subtype, n (%)	
antiMPO	17 (41)
antiPR3	18 (43)
antiPR3 + antiMPO	3 (7)
undifferentiated	4 (10)
Diagnosis, n (%)	
iRPGN	16 (38.09)
MPA	9 (21.43)
GPA	17 (40.48)
Affection of other organs, n (%)	
skin	5 (18.52)
lung	19 (70.37)
ORL	3 (11.11)
in total	27 (100)
Induction therapy, n (%)	
CYP	1 (2.4)
CS	3 (9.60)
CS+CYP	25 (59.50)
CS+CYP+PF	13 (31)
GFR (mL/min), min-max; mean ± SD	4-156; 52.71 (42.46)
Kidney function at the moment of disease presentation, n (%)	
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 (14.29)
CKD grade 5	12 (28.57)
Hemodialysis, n (%)	
iRPGN	2 (4.76)
MPA	6 (14.29))
GPA	4 (9.52)

Anti-MPO – anti-myeloperoxydase-antineutrophic antibodies;
anti-PR3 – anti-proteinase 3; iRPGN – idiopathic rapidly progressive glomerulonephritis;
MPA – microscopic polyangiitis; GPA – granulomatosis with polyangiitis;
CYP – cyclophosphamide; CS – corticosteroids; PF – physical therapy;
ORL – otorhinolaryngology; GFR – glomerular filtration rate;
CKD – chronic kidney disease; SD – standard deviation.

was: 5 procedures in patients with WG, 5 procedures in patients with MPA, 3 procedures in patient with iRPGN. Initially, 12 patients required heamodialysis treatment (2 patients with iRPGN, 6 patients MPA, 4 patients with WG). Twenty nine patients had a complete and 13 patients had partial remission. Table 1 presents the clinical characteristics of patients in the moment of disease presentation. The most common cause of hospitalization of patients with ANCA vasculitis were infections: urinary tract infections (in 11 patients), then lower respiratory tract infections (in 6 patients), and upper respiratory tract infections (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 WG). 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 WG). Seven of these patients were initially on haemodialysis, and cause of death was alveolar heamorrhage in 4 patients, and severe infections in 8 patients. Table 2 presents the clinical characteristics of patients after five-year follow-up period.

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 decreased 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 was concluded that the predictive GFR model in t = 5 was statistically significant. The cor-

Table 2

Clinical characteristics of patients after five-year follow-up period (t = 5)

Parameter	Values	
Infections	1	4.76
encephalitis	6	28.57
RTI	11	52.38
UTI	1	4.76
nediastinitis	6	28.57
ORL	21	100
in total		
GFR (mL/ min), min–max; mean ± SD	4–148; 58.21 ± 37.54	
Kidney function, n (%)		
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
Haemodialysis, n (%)	34	82.90
no	8	17.10
yes		
Mortality, n (%)	30	71.40
no	12	28.57
yes		

RTI – respiratory tract infections; UTI – urinary tract infections; CKD – chronic kidney disease; ORL – otorhinolaryngology; GFR – glomerular filtration rate.

Table 3

Predictive model for glomerular filtration rate at the moment of the disease presentation (t = 0)

Predictors	Coefficient β	*t*	*p*	95% CI	
Constant		4.143	0.000	72.039	240.803
Age	-0.390	-2.675	0.011	-3.147	-0.372

CI – confidence interval.

rected determination coefficient showed 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).

Table 4

Predictive model for glomerular filtration rate (GFR) after five-year follow-up period (t = 5)

Predictors	Coefficient β	*t*	*p*	95% CI	
Constant		0.532	0.598	-23.131	36.839
GFR	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

ANCA – anti-neutrophil cytoplasm antibody; CI – confidence interval.

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 [1], and for that reason, the accent on providing the better outcome should be focused on the treatment of renal vasculitis [19, 20]. 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 Walsch et al. [21], and prospective multicentric clinical study of de Lind van Wijngaarden et al. [22] (21%) and Titeca-Beauport et al. [23] (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 multinational randomized controlled study (MEPEX) study [24], 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 [25]. Other histological research did not prove the difference between antiPR3 and antiMPO antibodies [26]. In our study, we noticed that the subtypes of ANCA antibodies affected 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). Twenty one patients (50%) had renal-limited form of the disease, and in 19 patients (70.37%) lung damage was present. Infection is one of the main problems during the treatment of AAV, and also is the main cause of death in immunosuppressed patients [27–29]. Unlike the study of Kronbichler et al. [30], 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%, respectively [1, 31–33].

Conclusion

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.

R E F E R E N C E S

1. *Flossmann O, Berden A, de Groot K, Hagen C, Harper L, Heijl C*, et al. Longterm patient survival in ANCAassociated vasculitis. Ann Rheum Dis 2011; 70(3): 488–94.
2. *Chen M, Yu F, Zhang Y, Zhao MH*. Clinical [corrected] and pathological characteristics of Chinese patients with antineutrophil cytoplasmic autoantibody associated systemic vasculitides: A study of 426 patients from a single centre. Postgrad Med J 2005; 81(961): 723–7.
3. *Corral-Gudino L, Borao-Cengotita-Bengoa M, Del Pino-Montes J, Lerma-Márquez JL*. Overall survival, renal survival and relapse in patients with microscopic polyangiitis: A systematic review of current evidence. Rheumatology (Oxford) 2011; 50(8): 1414–23.
4. *Manno RL, Seo P, Geetha D*. Older patients with ANCA-associated vasculitis and dialysis dependent renal failure: a retrospective study. BMC Nephrol 2015; 16: 88.
5. *Berden AE, Ferrario F, Hagen EC, Jayne DR, Jennette JC, Joh K,* et al. Histopathologic classifcation of ANCA-associated glomerulonephritis. J Am Soc Nephrol 2010; 21(10): 1628–36.
6. *Chang DY, Wu LH, Liu G, Chen M, Kallenberg CG, Zhao MH*. Re-evaluation of the histopathologic classifcation of ANCA-associated glomerulonephritis: a study of 121 patients in a single center. Nephrol Dial Transplant 2012; 27(6): 2343–9.
7. *Quintana LF, Peréz NS, De Sousa E, Rodas LM, Griffiths MH, Solé M,* et al. ANCA serotype and histopathological classification for the prediction of renal outcome in ANCA-associated glomerulonephritis. Nephrol Dial Transplant 2014; 29(9): 1764–9.
8. *Tanna A, Guarino L, Tam FW, Rodriquez-Cubillo B, Levy JB, Cairns TD,* et al. Long-term outcome of anti-neutrophil cytoplasm antibody-associated glomerulonephritis: Evalua-

tion of the international histological classifcation and other prognostic factors. Nephrol Dial Transplant 2015; 30(7): 1185–92.
9. *Booth AD, Almond MK, Burns A, Ellis P, Gaskin G, Neild GH,* et al. Outcome of ANCA-associated renal vasculitis: A 5-year retrospective study. Am J Kidney Dis 2003; 41(4): 776–84.
10. *Fauci AS, Wolf SM*. Wegener's granulomatosis: studies in eighteen patients and a review of the literature. Medicine (Baltimore) 1973; 52(6): 535–61.
11. *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 2005; 143(9): 621–31.
12. *Pierrot-Deseilligny Despujol C, Pouchot J, Pagnoux C, Coste J, Guillevin L*. Predictors at diagnosis of a first Wegener's granulomatosis relapse after obtaining complete remission. Rheumatology (Oxford) 2010; 49(11): 2181–90.
13. *Tan JA, Dehghan N, Chen W, Xie H, Esdaile JM, Avina-Zubieta JA*. Mortality in ANCA-associated vasculitis: a meta-analysis of observational studies. Ann Rheum Dis 2017; 76(9): 1566–74.
14. *Moosig F, Bremer JP, Hellmich B, Holle JU, Holl-Ulrich K, Laudien M*, et al. A vasculitis centre based management strategy leads to improved outcome in eosinophilic granulomatosis and polyangiitis (Churg-Strauss, EGPA): monocentric experiences in 150 patients. Ann Rheum Dis 2013; 72(6): 1011–7.
15. *Watanabe K, Tani Y, Kimura H, Tanaka K, Hayashi Y, Asahi K*, et al. Clinical outcomes of Japanese MPOANCA related nephritis: Significance of initial renal death for survival. Intern Med 2012; 51(15): 1969–76.
16. *Li ZY, Gou SJ, Chen M, Zhao MH*. Predictors for outcomes in patients with severe ANCAassociated glomerulonephritis who were dialysisdependent at presentation: A study of 89 cases in a single Chinese center. Semin Arthritis Rheum 2013; 42(5): 515–21.
17. *Holle JU, Gross WL, Latza U, Nölle B, Ambrosch P, Heller M,* et al. Improved outcome in 445 patients with Wegener's granulomatosis in a German vasculitis center over four decades. Arthritis Rheum 2011; 63(1): 257–66.
18. *Takala JH, Kautiainen H, Leirisalo-Repo M*. Survival of patients with Wegener's granulomatosis diagnosed in Finland in 1981-2000. Scand J Rheumatol 2010; 39(1): 71–6.
19. *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 2013; 65(1): 1–11.
20. *Cockcroft DW, Gault MH*. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16(1): 31-41.
21. *Walsh M, Casian A, Flossmann O,Westman K, Höglund P, Pusey C,* et al. Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear. Kidney Int 2013; 84(2):397–402.
22. *de Lind van Wijngaarden RA, Hauer HA, Wolterbeek R, Jayne DR, Gaskin G, Rasmussen N,* et al. Clinical and histologic determinants of renal outcome in ANCA-associated vasculitis: A prospective analysis of 100 patients with severe renal involvement. J Am Soc Nephrol 2006; 17(8): 2264–74.
23. *Titeca-Beauport D, Francois A, Lobbedez T, Guerrot D, Launay D, Vrigneaud L,* et al. Early predictors of one-year mortality in patients over 65 presenting with ANCA-associated renal vasculitis: a retrospective, multicentre study. BMC Nephrol 2018; 19(1): 317.
24. *Jayne DR, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L,* et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol 2007; 18(7): 2180–8.
25. *de Joode AA, Sanders JS, Stegeman CA*. Renal survival in proteinase 3 and myeloperoxidase ANCA-associated systemic vasculitis. Clin J Am Soc Nephrol 2013; 8(10): 1709–17.
26. *Vergunst CE, van Gurp E, Hagen CE, van Houwelingen HC, Hauer HA, Noël LH*, et al. An index for renal outcome in ANCA-associated glomerulonephritis. Am J Kidney Dis 2003; 41(3): 532–8.
27. *Charlier C, Henegar C, Launay O, Pagnoux C, Berezne A, Bienvenu B*, et al. Risk factors for major infections in Wegener granulomatosis: analysis of 113 patients. Ann Rheum Dis 2009; 68(5): 658–63.
28. *Reinhold-Keller E, Beuge N, Latza U, de Groot K, Rudert H, Nolle B,* et al. An interdisciplinary approach to the care of patients with Wegener's granulomatosis-long-term outcome in 155 patients. Arthritis Rheum 2000; 43(5): 1021–32.
29. *Gavraud M, Guillevin L, Le Toumelin P, Cohen P, Lhote F, Casassus P,* et al. Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome. Analysis of four prospective trials including 278 patients. Arthritis Rheum 2001; 44(3): 666–75.
30. *Kronbichler A, Jayne DR, Mayer G*. Frequency, risk factors and prophylaxis of infection in ANCA-associated vasculitis. Eur J Clin Investig 2015; 45(3): 346–68.
31. *McGregor JC, Negrete-Lopez R, Poulton CJ, Kidd JM, Katsanos SL, Goetz L*, et al. Adverse events and infectious burden, microbes and temporal outline from immunosuppressive therapy in antineutrophil cytoplasmic antibody-associated vasculitis with native renal function. Nephrol Dial Transplant 2015; 30(Suppl1): 171–81.
32. *Kitagawa K, Furuichi K, Sagara A, Shinozaki Y, Kitajima S, Toyama T,* et al. Risk factors associated with relapse or infectious complications in Japanese patients with microscopic polyangiitis. Clin Exp Nephrol 2016; 20(5):703–11.
33. *Wall N, Harper L*. Complications of long-term therapy for ANCA-associated systemic vasculitis. Nat Rev Nephrol 2012; 8(9): 523–32.

Received on September 23, 2019
Revised on November 21, 2019
Accepted on November 25, 2019
Online First November, 2019