

Article

Kidney pathology and outcomes in ANCA-associated vasculitis: retrospective analysis of 85 patients

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Abstract: ANCA-associated vasculitis (AAV) pose a significant risk of kidney failure, kidney biopsy remains a key prognostic tool. Pathology classification of the AAV glomerulonephritis (GN) developed by Berden et al showed correlation between GN classes and kidney outcomes; ANCA Renal Risk Score (ARRS) included tubular atrophy and interstitial fibrosis (TA/IF) as an additional parameter for risk assessment. We aimed to evaluate kidney survival across AAV GN classes and ARRS groups. A single-center retrospective study included 85 adult patients with biopsy-proven AAV kidney disease followed in 2000-2020. Primary outcome was kidney survival at the end of 18 [5; 66] months follow-up, kidney death considered as CKD stage 5. We found significant difference in the kidney survival for sclerotic, mixed, crescentic and focal AAV GN classes: 19%, 76.2%, 91.7% and 100% respectively ($p=0.009$). Kidney survival was 0%, 75.6% and 100% for the high, medium and low risk ARRS groups respectively ($p<0.001$); TA/IF analysis showed kidney survival 49.6% vs 87.7% for widespread and mild TA/IF respectively ($p=0.003$). Kidney survival was significantly lower in anti-MPO-ANCA versus anti-PR3-ANCA carriers (50.3% and 78.1% respectively, $p=0.045$). We conclude that unfavorable AAV kidney outcomes associated with sclerotic GN class by Berden's classification, ARRS high risk group, and anti-MPO-ANCA subtype.

Keywords: microscopic polyangiitis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, kidney biopsy, pauci-immune focal and segmental necrotizing and crescentic glomerulonephritis, tubular atrophy and interstitial fibrosis, kidney survival

1. Introduction

ANCA-associated vasculitis (AAV) pose a significant risk of kidney failure; frequency of kidney involvement in AAV varies from 90% in Microscopic Polyangiitis (MPA) and 80% in Granulomatosis with Polyangiitis (GPA) to 45% in Eosinophilic Granulomatosis with Polyangiitis (EGPA) [1, 2]. Therefore, kidney survival remains one of the most important outcomes in AAV. A systematic review of 44 studies, performed in 2008 by the European Vasculitis Study Group found valuable data for GPA only, with kidney survival 93% and 85% for 1-year and 5-years respectively; the data for MPA and EGPA were scarce. [3]. Eight years later a multicenter study of 144 patients with MPA managed according to the EULAR recommendations [4] showed that chronic kidney disease (CKD) stage 5 developed in 7.6% of patients with median follow-up 33.5 months [5]. However, another study, including 80% of patients with MPA or renal-limited AAV demonstrated less optimistic results – 47% of patients reached CKD stage 5 by the end of 5-year follow-up period [6]. A study of the Asian population confirmed unfavorable kidney outcomes for MPA – 30.1% of patients reached a composite end-point (doubling

of serum creatinine or CKD stage 5) during 17 months regardless of the immunosuppressive treatment [7]. In contrast, the most recent data concerning kidney survival in EGPA, and provided by the retrospective study of 63 patients, show that just 17% of patients reached CKD stage 5 with median follow-up 48 months [8].

Evaluation of ANCA titers in association with kidney outcomes did not show direct correlation between clinical remission and decrease of ANCA levels [9]; and the role of ANCA subtype remains controversial. A review, published in 2016, concluded that anti-proteinase3 (anti-PR3) subtype of ANCA associated with higher risk of relapses [10]. Later, a single-center study of 85 patients with AAV confirmed that anti-myeloperoxidase (anti-MPO) subtype of ANCA associated with the lower risk for relapse, but with the worst patients and kidney survival; additional unfavorable prognostic factors included older age at the disease onset and male gender [11]. The most recent publication of the long-term observation of patients with AAV demonstrated that recurrent or persistent ANCA-positivity associated with worst kidney outcomes, and recurrent pattern of the anti-MPO-AAV associated with worsening kidney function [12].

The patients with AAV, especially those with severe kidney disease remain at high risk of unfavorable outcomes despite currently available effective treatments [2, 9, 13-16]. Even though prognostic value of ANCA titer and subtype and several other biomarkers, as well as the role of treatment and therapeutic strategies had been extensively studied in association with kidney outcomes over last decades, kidney biopsy remains a key diagnostic and prognostic tool, in particular for ANCA-negative and renal-limited AAV [17]. The characteristic kidney lesion in AAV is pauci-immune focal and segmental necrotizing and crescentic glomerulonephritis (GN), however, pathology features vary from mild focal segmental extracapillary proliferation to diffuse crescentic GN and interstitial granulomas or infiltrates [18, 19]. Moreover, differential diagnosis between GPA, EGPA and MPA is based, above all, on the presence or absence of the granulomatous inflammation, as it is stressed in the statements of the Chapel-Hill Consensus Conference 2012 [20] as well as in the algorithms of the European Medical Agency (EMA) [21].

Pathology classification of the AAV GN, proposed by Berden et al, demonstrated a correlation between GN classes and kidney outcomes [22]. This classification distinguishes four classes: focal ($\geq 50\%$ of normal glomeruli), extracapillary or crescentic ($\geq 50\%$ of the glomeruli with cellular crescents), sclerotic ($\geq 50\%$ of totally sclerosed glomeruli), and mixed; interstitial damage did not show significant influence on the kidney failure rate, which initially lead to the conclusion that glomerular damage plays a key role [22]. However later the same group showed that tubular atrophy and necrosis were significant predictors of the decline of kidney function [23]. Last decade several other histological classifications for renal AAV had been proposed and validated [24-27]. Thus, recently developed clinicopathologic ANCA Renal Risk Score (ARRS) for prediction of renal outcome in AAV GN includes tubular atrophy and interstitial fibrosis (TA/IF) as one of the parameters for the risk assessment. Proposed and validated parameters are the percentage of normal glomeruli (N: 0-4-6 points), percentage of TA/IF (T: 0-2 points), and glomerular filtration rate (GFR) (G: 0-3 points); calculated sum of points distinguishes three risk groups: low (0 points), medium (2-7) points, and high (8-11 points) [28]. In addition, the higher percentage of normal glomeruli was found in the biopsies of patients with the comparable GFR level at the time of kidney biopsy and anti-PR3 subtype versus anti-MPO subtype. Anti-MPO-ANCA also was associated with the higher extent of fibrotic lesions - both glomerulosclerosis and interstitial fibrosis [29, 30].

In this retrospective study of AAV kidney outcomes, we aimed to evaluate kidney survival in association with GN class according Berden's classification, with the ARRS group, and with the ANCA subtypes.

2. Materials and Methods

A single-center retrospective study, using electronic database, identified 121 patients ≥ 18 years old with AAV, diagnosed in our center in 2000-2020 according to the ACR [31] criteria and EMA algorithm [21]. For the purpose of this study, the main data retrieved were age, gender, main diagnosis, systemic signs and symptoms and serum creatinine at presentation, disease activity, ANCA levels and subtype, date of kidney biopsy, kidney pathology findings, initial and subsequent treatment regimens, follow-up duration, and eGFR at the end of the follow-up.

Ultrasound-guided kidney biopsy was performed according the standard in-hospital protocol, with specimen handling and pathology evaluation in the dedicated kidney pathology unit. For light microscopy, sections of formalin fixed paraffin-embedded tissue stained with H&E, Masson's trichrome, periodic acid-Schiff and Congo Red. Immunofluorescence was performed on frozen sections with FITS-conjugated antibodies to IgA, IgG, IgM, C1q, C3, fibrinogen, lambda and kappa light chains. ANCA levels tested using immunoenzyme assay or indirect immunofluorescence. Disease activity was scored at the time of diagnosis basing on the Birmingham Vasculitis Activity Index (BVAS v.3) [32]. Pattern and severity of kidney disease was evaluated according to the Berden's classification and ARRS [22, 28].

After evaluation of clinical, serology and pathology findings 36 patients with dual phenotype (both ANCA and anti-GBM positivity) or with AAV, superimposed on IgA-vasculitis, and cases without adequate kidney pathology data (less than 5 glomeruli in the biopsy specimen) were excluded from further analysis (Figure 1). The median number of glomeruli per specimen in the study group was 13 [12; 19], 82 out of 85 cores contained ≥ 10 glomeruli, and only 3 cores contained 7 and 6 glomeruli respectively. Study group comprised 85 patients with pathology-proven AAV kidney disease, including 51 (60%) females and 34 (40%) males, median age 55.5 [41; 61.7] years. GPA was diagnosed in 34 (40%) patients, MPA – in 44 (51.8%) patients, and EGPA – in 7 (8.2%) of patients.

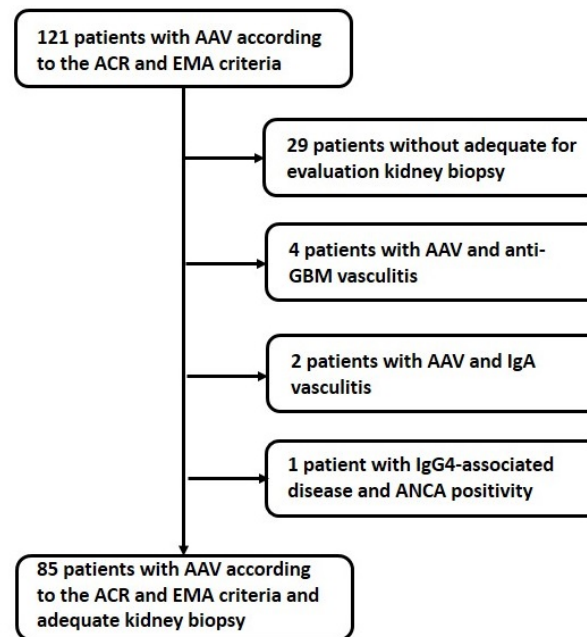


Figure 1. Study group selection

Initial treatment regimens included glucocorticoids plus intravenous cyclophosphamide in 57 (67%) cases, glucocorticoids plus rituximab in 12 (14.1%) cases, and glucocorticoids plus cyclophosphamide followed by rituximab in 16 (18.8%) cases. 7 patients presented with pulmonary hemorrhage received plasma exchanges. Subsequent treatment regimens included low doses of glucocorticoids combined with azathioprine or methotrexate for patients, who initially received cyclophosphamide. Patients, who received rituximab for initial treatment, continued on rituximab.

Primary outcome was kidney death at the end of follow-up. The end of follow-up was defined as a date of the last visit or the date of patient's death. Kidney death was considered as CKD stage 5 (eGFR <15 ml/min/1.73 m² CKD-EPI equation) regardless the demand for kidney replacement therapy.

The data presented as number (percentage) for categorical variables and median [interquartile range (IQR)] for continuous variables. *Spearman's rank correlation coefficient* used for statistical correlations. Kidney survival rate was assessed using the Kaplan-Meier method. Differences between categories assessed using the log-rank test; p value < 0.05 was considered as significant. The data analysis performed on a personal computer using statistical package IBM SPSS Statistics v 23.

3. Results

3.1. Main disease characteristics

Elevated ANCA levels found in 77 (90.6%) of patients, 42 of which had anti-MPO-ANCA, 25 – anti-PR3-ANCA, and in 10 cases screening test for ANCA using indirect immunofluorescence was performed without identification of ANCA subtype; 8 patients (9.4%) had seronegative AAV. All patients had severe disease with median BVAS score 15 [12.3; 19.8] at the time of diagnosis. Systemic features and kidney pathology shown in the Table 1.

Table 1. Clinical manifestations and kidney pathology

Systemic features	All patients (85)	Anti-PR3 positive (25)	Anti-MPO positive (42)	ANCA screening test positive (10)	Sero- negative (8)
Lungs, N (%)					
<i>Interstitial lung damage</i>	22 (25.9)	8 (32)	3 (30.9)	2 (20)	0 (0)
<i>Infiltrates</i>	16 (18.8)	3 (12)	8 (19)	4 (40)	1 (12.5)
<i>Cavities</i>	3 (3.5)	3 (12)	0 (0)	2 (20)	0 (0)
<i>Nodular masses</i>	3 (3.5)	2 (8)	1 (2.4)	0	1 (12.5)
<i>Asthma</i>	7 (8.2)	2 (8)	4 (9.5)	1 (10)	2 (25)
<i>Hemoptysis, pulmonary hemorrhage</i>	11 (12.9)	3 (12)	6 (14.3)	1 (10)	1 (12.5)
Skin, N (%)	22 (25.8)	6 (24)	16 (38.1)	2 (20)	1 (12.5)
Joints, N (%)	27 (31.7)	11 (44)	12 (28.6)	2 (20)	2 (25)
Gastrointestinal, N (%)	6 (7.0)	2 (8)	3 (7.1)	1 (10)	1 (12.5)
Nervous system, N (%)	12 (14.1)	6 (24)	5 (11.9)	0	1 (12.5)
ENT, N (%)	38 (44.7)	19 (76)	16 (38.1)	2 (20)	4 (50)
Eyes, N (%)	13 (15.3)	8 (32)	4 (9.5)	0 (0)	1 (12.5)
BVAS v.3 at presentation	15.0 [12.9; 19.8]	15 [14; 20]	15 [13; 20]	14 [13; 18.5]	18 [11; 20.5]
Median serum creatinine at presentation, $\mu\text{mol/L}$	257.0 [171.0; 528.5]	203 [130; 311]	139 [120; 347]	250 [151.5; 576]	100 [73; 308.5]
Kidney pathology (Berden's classification)					
<i>Focal, N (%)</i>	20 (23.5)	3 (12)	11 (26.2)	3 (30)	3 (37.5)
<i>Crescentic, N (%)</i>	22 (25.9)	8 (32)	9 (21.4)	3 (30)	2 (25)
<i>Mixed, N (%)</i>	18 (21.2)	7 (28)	9 (21.4)	2 (20)	0 (0)
<i>Sclerotic, N (%)</i>	24 (28.2)	7 (28)	12 (28.6)	2 (20)	3 (37.5)
ARRS					
<i>Low, N (%)</i>	22 (25.9)	7 (28)	9 (21.4)	2 (20)	4 (25)
<i>Medium, N (%)</i>	42 (49.4)	12 (48)	21 (50)	6 (60)	3 (37.5)
<i>High, N (%)</i>	21 (24.7)	6 (24)	12 (28.6)	2 (20)	1 (12.5)

Median serum creatinine at presentation was 257.0 [171; 528.5] $\mu\text{mol/L}$. According to Berden's classification 20 patients had focal GN, 22 – crescentic GN, 18 – mixed GN, and 24 – sclerotic GN class; a single patient with severe kidney and lung involvement had interstitial nephritis without glomerular damage. Median ARRS in the main study group was 4 points [2.0; 6.0]; while 21 patients had high risk, 42 patients – medium risk, and 22 – low risk according to the ARRS.

Follow-up duration did not differ significantly between patients with GPA, MPA and EGPA. By the end of the follow-up period 66 (77.6%) patients achieved remission, 12

(14.1%) patients with remission of extrarenal manifestations developed ESKD and received dialysis treatment, and 7 (8.2%) patients did not achieve remission and died from extra-renal complications.

3.2. Kidney survival analysis in the main study group

At the end of the follow-up with the median of 18 [5; 66] months, patient's survival was 89.5%, and kidney survival - 75.4%. Patients of more advanced age at the disease onset had more advanced CKD stages by the end of the follow-up period ($r=0.303$; $p=0.011$). Comparison of kidney outcomes in 2000-2010 and 2011-2020 did not show significant differences, kidney death occurred in 26.6% and 23.6% of cases respectively ($\chi^2=0.098$, $p=0.754$).

Analysis of the outcomes for AAV GN classes defined according to Berden's classification showed significant difference in the kidney survival between all four classes: 19%, 76.2%, 91.7% and 100% for sclerotic, mixed, crescentic and focal class respectively ($p=0.009$) (Figure 2).

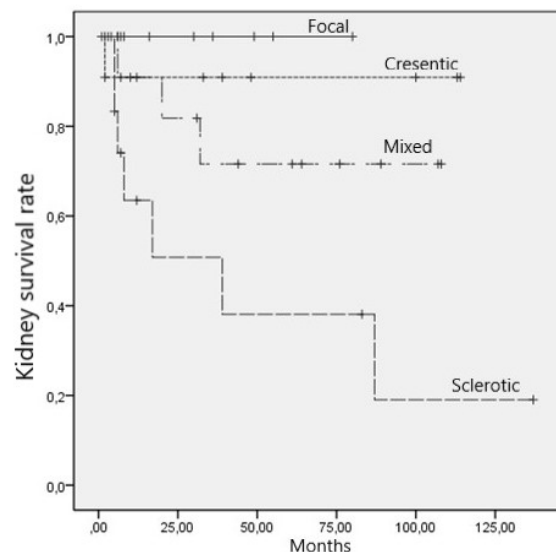


Figure 2. Kidney survival in the different classes of ANCA-associated glomerulonephritis according to Berden's classification ($p=0.009$)

Among 57 patients, who received cyclophosphamide followed by azathioprine or methotrexate, kidney survival was 33%, 75%, 86.7% and 100% for sclerotic, mixed, crescentic and focal class respectively ($p=0.004$). In 12 patients, who received rituximab only, kidney survival was 0% for sclerotic class and 100% for mixed, crescentic and focal classes ($p=0.015$). In the patients, switched from cyclophosphamide to rituximab, kidney survival was 62% for sclerotic class, 0% for mixed class, and 100% for focal and crescentic classes ($p=0.033$).

We found statistically significant correlation between median ARRS at presentation and CKD stage at the end of follow-up ($r=0.490$, $p<0.001$). High ARRS group demonstrated unfavorable kidney outcome – kidney survival was 0%, 75.6% and 100% for the high, medium and low groups respectively ($p<0.001$) (Figure 3).

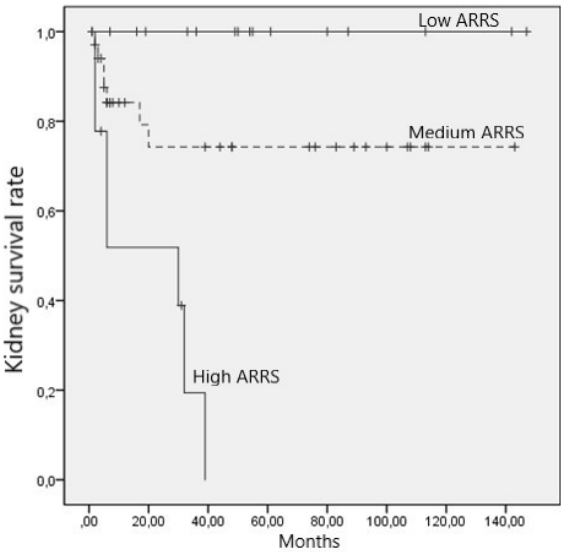


Figure 3. Kidney survival according to the ARRS group (Low 0-1 points: Medium 2-7 points: High 8-11 points) ($p<0.001$)

In addition, kidney survival was 0% and 100% for low and high risk group respectively regardless the treatment regimen. In the medium risk group, kidney survival was 100% in the patients, who received rituximab only or were switched from cyclophosphamide to rituximab and continued on rituximab, and 81.8% in the patients who received cyclophosphamide followed by azathioprine or methotrexate ($p=0.438$).

Using ARRS parameters, we evaluated the degree of TA/IF and of the glomerular damage separately, and found that the patients with the widespread TA/IF reached CKD stage 5 significantly more often compared to those with mild TA/IF: kidney survival was 49.6% vs 87.7% for T2 and T0 points respectively ($p=0.003$) (Figure 4).

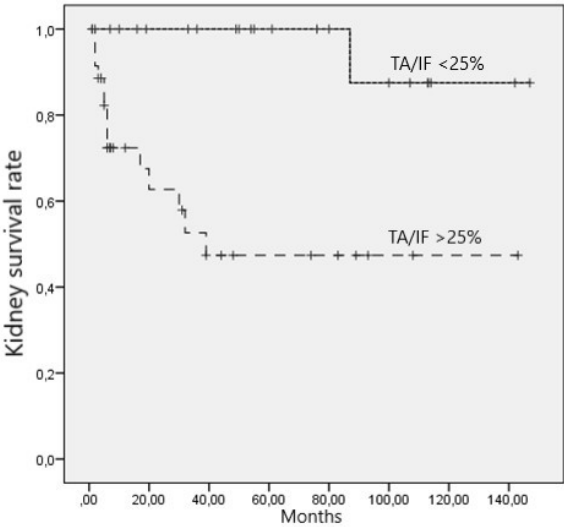


Figure 4. Kidney survival according to the tubular atrophy and interstitial fibrosis ARRS points (T0 < 25%; T2 > 25%) ($p=0.003$)

Similarly, the patients with the higher number of damaged glomeruli reached CKD stage 5 significantly more often, compared to those with the lower number of damaged glomeruli: kidney survival 30%, 43.2% and 78.1% for N6, N4 and N0 points respectively ($p=0.001$) (Figure 5).

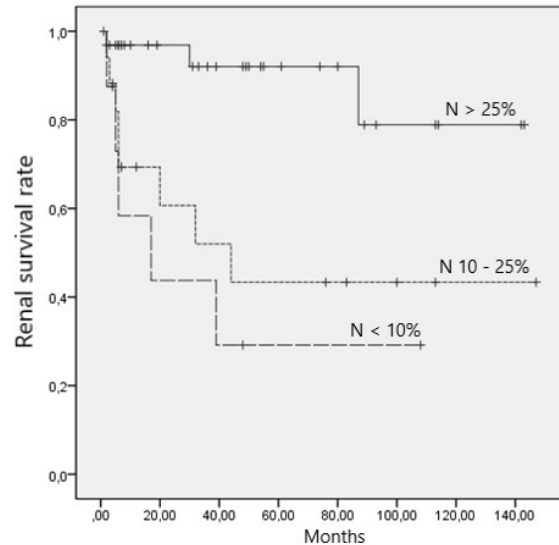


Figure 5. Kidney survival according to the percentage of normal glomeruli ARRS points (N0 >25%; N4 10-25%; N6 <10%) ($p=0.001$)

Finally, kidney survival was significantly lower in patients anti-MPO-ANCA compared to those with anti-PR3-ANCA (50.3% vs 78.1% respectively, $p=0.045$) (Figure 6).

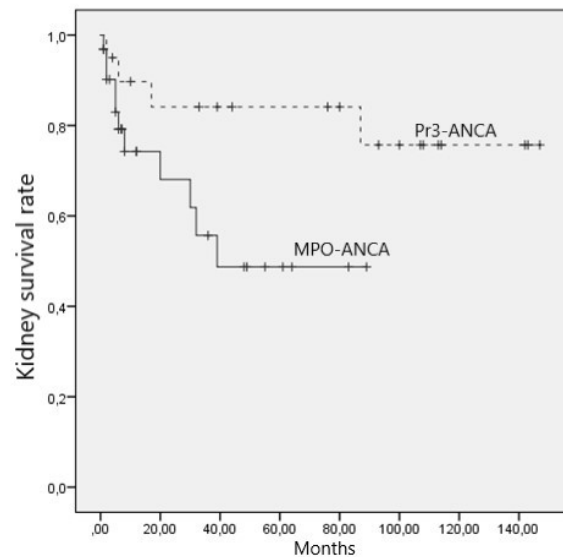


Figure 6. Kidney survival in the patients with anti-MPO-ANCA versus anti-PR3-ANCA ($p=0.045$)

3.3. Kidney survival analysis in the anti-PR3-ANCA and anti-MPO-ANCA subgroups

Given the different renal outcomes in the patients with anti-PR3 and anti-MPO-ANCA in the main group, we divided patients with available ANCA subtype data into 2 subgroups – anti-MPO and anti-PR3 ANCA carriers. The results of analysis according to the Berden's classification in the subgroups tend to be close to the general study group; however, we did not find statistically significant differences for all four classes in the particular subgroups. Kidney survival in the anti-PR3-ANCA subgroup was similarly high (100%) for crescentic and focal classes, and in the anti-MPO-ANCA subgroup – almost similarly low (24.3% and 31%) for sclerotic and mixed classes respectively.

In contrast, analysis according to the ARRS showed statistically significant differences within the ANCA subtypes subgroups. In the anti-PR3-ANCA subgroup, kidney survival was 0%, 82.5% and 100% ($p=0.019$) (Figure 7); and in the anti-MPO-ANCA subgroup it was 0%, 41.8% and 100% ($p=0.028$) for the high, medium and low risk respectively (Figure 8).

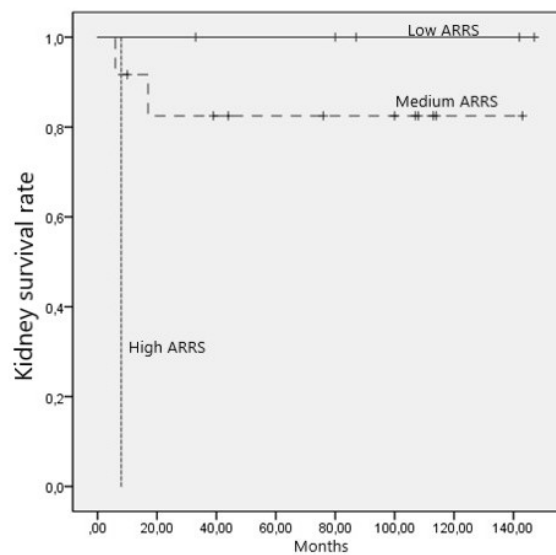


Figure 7. Kidney survival according to the ARRS score in the anti-PR3 subgroup ($p=0.019$)

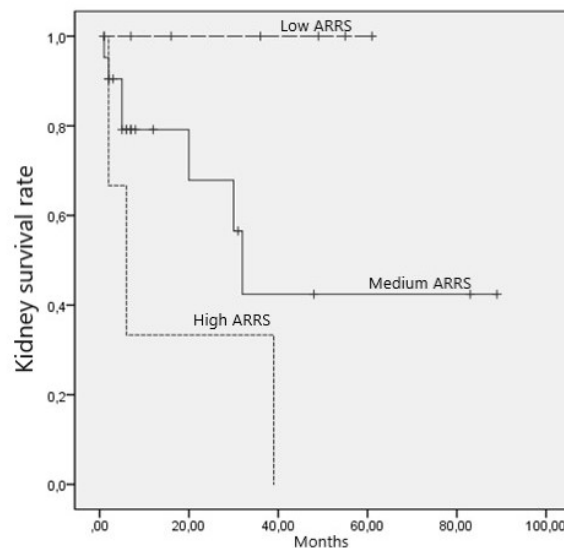


Figure 8. Kidney survival according to the ARRS score in the anti-MPO subgroup ($p=0.028$)

Kidney survival in the low and high ARRS risk groups did not differ significantly in both ANCA subtypes sub-groups. However, the patients with the medium ARRS risk and anti-MPO-ANCA had worse kidney survival compared to the medium ARRS risk and anti-PR3-ANCA (41.8% vs 82.5% respectively), even though the differences did not reach statistical significance ($p=0.13$).

4. Discussion

Patients with AAV remain at high risk of unfavorable outcomes despite currently available effective treatments [2-8], and evaluation of the prognostic factors for kidney outcomes at the time of diagnosis plays a key role. Kidney pathology not only confirm the diagnosis, but also predict kidney survival and thus, guide the treatment strategy. Even though Berden's classification of the AAV GN clearly distinguishes focal and active lesions from diffuse and chronic, and demonstrates the impact of glomerular sclerosis on the kidney outcome, this classification does not accommodate TA/IF. However, the degree of tubulointerstitial damage and its role in CKD progression for glomerular diseases is well established [33-35] and the ARRS score main advantage is incorporation of both glomerular and tubulointerstitial lesions.

In our study group kidney survival by the end of the follow-up of 18 [5; 66] months was 75.4%, which is comparable to the most recent data [16]. We used both Berden's classification and ARRS to evaluate kidney pathology prognostic value. Our results consistent with the Berden's original publication data [22]: in our study group the focal class, as expected, had the best outcome, and sclerotic class – the worst outcome. Of note, not all validation studies confirmed the difference between crescentic and mixed classes, thus a large meta-analysis, including 1601 patients, did not show significant differences in the progression to CKD stage 5 between these classes (RR 1.14, 95% CI 0.91-1.43, $p=0.27$) [36]. In our study, kidney survival in the crescentic class turned significantly better compared to the mixed class in the general group, confirmed by the analysis in the anti-MPO-ANCA and anti-PR3 subgroups. Importantly, we found significantly worse kidney survival in the anti-MPO-ANCA carriers regardless kidney pathology findings, which confirms the negative impact of anti-MPO-ANCA on kidney outcomes [18, 19, 29, 30, 37]. Comparison of kidney survival across the Berden's classification and according to treatment regimens did not show significant differences between the main study group and the group of patients, who received initial treatment with cyclophosphamide. It was 19%, 76.2%, 91.7% and 100% for sclerotic, mixed, crescentic and focal class respectively for the main group and 33%, 75%, 86.7% and 100% for sclerotic, mixed, crescentic and focal class respectively for the cyclophosphamide subgroup. However, the patients, who received rituximab or were switched from cyclophosphamide to rituximab due to the lack of cyclophosphamide efficacy, demonstrated 100% kidney survival not only for the focal, but also for the crescentic class, which means that rituximab may be more effective than cyclophosphamide for the treatment of the active lesions.

The results of ARRS analysis in our study also consistent with the original publication [28] data; we found that kidney survival in the high ARRS group was not surprisingly the worst. Worthy to note, that the separate evaluation of glomerular and tubulointerstitial lesions confirmed significant differences in the kidney survival depending both on N (percentage of normal glomeruli) and T (percentage of TA/IF) parameters. There are some data concerning isolated tubulointerstitial damage in AAV [38], however in our group, just one patient did not have glomerular lesions, which did not allow analyzing this pattern. Additional finding in our study was the worse kidney survival within the medium ARRS risk group in the anti-MPO-ANCA carriers versus anti-PR3-ANCA carriers. The difference did not reach statistical significance, and the possible explanation refer to the data indicating that severe active lesions at the disease onset in anti-PR3 AAV may flatten the differences in prognostic value of ANCA subtypes [39, 40]. However, summarizing the available data Kronbichler and Jane [41] stressed the association of the

anti-MPO-ANCA subtype with TA/IF, tubular necrosis, and glomerulosclerosis. Importantly, kidney survival in our study did not depend on the treatment regimen across the ARRS groups, confirming that ARRS, which includes tubulointerstitial damage and eGFR, is the most effective tool for prediction of the kidney outcomes.

5. Conclusions

Our study confirms that unfavorable renal outcomes for AAV kidney disease associated with sclerotic class according to the AAV GN Berden's classification, ARRS high risk group, and presence of anti-MPO-ANCA; and demonstrates strength of ARRS for selected groups of patients.

Author Contributions: Conceptualization, E.Z. and A.Z.; methodology, E.Z. and A.Z.; software, A.Z.; formal analysis, A.Z.; investigation, E.Z., T.M., E.L. and E.S.; resources, E.Z., E.S., T.M. and E.L.; data curation, E.Z. and A.Z.; writing—original draft preparation, A.Z.; writing—review and editing, E.Z.; visualization, A.Z.; supervision, E.Z. and E.S. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent for kidney biopsy was obtained from all the patients prior to the procedure according to the in-hospital protocol. Patient consent for participation in this particular study was waived due to the retrospective nature of the study, not including any personal data.

Data Availability Statement: The data source is the patient's electronic records in the nephrology and kidney pathology units' database, which contain personal information and thus cannot be shared.

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