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# Clinical characteristics and long-term survival differences of the ANCA-associated vasculitis group: a cross-sectional study of 27 patients

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**Objective.** The goal of this study was to describe long-term patient survival and possible prognostic factors of a group of patients diagnosed with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) hospitalized at the tertiary Rheumatology Centre in Vilnius.

**Material and Methods.** A cross-sectional study of 27 patients hospitalized at the Rheumatology Centre of Santaros klinikos of Vilnius University Hospital from 1 January 2001 to 31 December 2015 with diagnoses of GPA and MPA were carried out. Data on demographics, clinical characteristics, laboratory data, and the Birmingham Vasculitis Activity Score were collected.

**Results.** Seven (25.9%) patients during the onset of the disease received only oral glucocorticoids and 20 (74.1%) patients took additional medication. The BVAS median was 7 (minimum [min] – 2; maximum [max] – 23). The age median was 52 years (min – 12; max – 75). The overall mortality rate was 18.5%. Mean survival time was 126.6 months (95% confidence interval [CI] = 104.5 to 148.6) limited to 154.6 months for the longest-surviving patient.

**Conclusions.** Life expectancy during past 15 years for AAV patients increased from 99.4 to 126.6 months. A high BVAS score at the onset of the disease is a bad prognostic factor related to shorter life expectancy. The growth of *Staphylococcus aureus* from nasopharynx might be associated with higher mortality rates and relapses in AAV patients.

**Keywords:** ANCA-associated vasculitis, outcomes, microscopic polyangiitis, granulomatosis with polyangiitis, BVAS score, life expectancy

## INTRODUCTION

According to the 2012 Revised International Chapel Hill Consensus, granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are assigned to the group of ANCA-associated vasculitis (AAV) (1). It is a rare group of diseases with an overall annual incidence of 11.3/one million for GPA and 5.9/one million for MPA (2). Primary systemic vasculitides produce an inflammation of blood vessels resulting in an occlusive, stenotic, or aneurysmal change leading to

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ischaemic or haemorrhagic events (3, 4). Both MPA and GPA predominantly affect small vessels and are associated with antineutrophil cytoplasmic autoantibodies (ANCA) specific for myeloperoxidase (MPO-ANCA) or proteinase 3 (PR3-ANCA) (1). MPA and GPA are a necrotizing vasculitis that induce glomerulonephritis and/or pulmonary capillaritis (1, 5). Moreover, they can involve a huge variety of other organs, including accessory organs of the eye, the central nervous system, upper airways, or even genitals (4, 6–8). Systemic features like fever, arthralgias, malaise, weight loss, and fatigue may be present (4). Treatment of AAV during recent years has changed significantly (3, 9, 10). However, despite recent advances in diagnosis and treatment, patients with AAV continue to have a substantially higher mortality than a matched general population (11). The goal of the study was to describe long-term patient survival and possible prognostic factors of a group of patients with GPA and MPA at the onset of the diseases who were hospitalized at the tertiary Rheumatology Centre in Vilnius.

## MATERIALS AND METHODS

A cross-sectional study of patients hospitalized at the Rheumatology Centre of Santaros klinikos of Vilnius University Hospital from 1 January 2001 to 31 December 2015 with diagnoses of granulomatosis with polyangiitis (Wegener) and microscopic polyangiitis was carried out. The diagnoses were confirmed by combining clinical assessment, serological tests for ANCA, and histological analysis. We included 24 patients with diagnoses of granulomatosis with polyangiitis and three patients with diagnoses of microscopic polyangiitis. All patients received treatment from the onset of the disease; the treatment included oral glucocorticoids. Data on demographics (gender, age, date of the first and last visit or death), clinical characteristics (organ involvement at the onset of the disease and immunosuppressive therapy), and laboratory data (C reactive protein, erythrocyte sedimentation rate, white blood cell count, platelet count, haemoglobin level, cANCA, creatinine level, and the growth of *Staphylococcus aureus* from the nasopharynx) were collected. The BVAS (Birmingham Vasculitis Activity Score) was calculated for each patient during the first visit. According to the result, we divided patients into two categories (score <10 and ≥10).

We defined the pulmonary insufficiency as a condition when the patient felt shortening of breath at a minimal psychical activity, and the renal insufficiency as a condition when the patient needed haemodialysis.

We considered that a patient recovered when his/her health condition remained stable without glucocorticoids and immunosuppressants for at least one year.

## STATISTICAL METHODS

Descriptive statistics were used to evaluate demographic and clinical characteristics. The survival was evaluated using Kaplan-Maier curves. The Cox regression was performed to evaluate differences between BVAS groups. Statistical analysis was performed using IBM SPSS (Statistical Package for the Social Sciences) version 22. A $p$ value of 0.05 was used to determine the level of statistical significance.

## RESULTS

Clinical and demographic characteristics are shown in Table 1. The number of cases is presented in Fig. 1.

**Table 1.** Clinical and demographic characteristics at the onset of the disease

| | ***n* = 27** |
|---|---|
| **Age:** | |
| <65 years | 20 (74.1%) |
| ≥65 years | 7 (25.9%) |
| **Gender:** | |
| Male | 9 (33.3%) |
| Female | 18 (66.7%) |
| **BVAS:** | |
| <10 | 18 (66.7%) |
| ≥10 | 9 (33.3%) |
| **cANCA:** | |
| Positive | 15 (55.6%) |
| Negative | 12 (44.4%) |
| ***S. aureus:*** | |
| Positive | 11 (40.7%) |
| Negative | 13 (48.1%) |
| Data not known | 3 (11.1%) |

| | |
|---|---|
| **Outcome on 31 December 2015** | |
| Death | 5 (18.5%) |
| Recovered | 4 (14.8%) |
| Still treated | 18 (66.7%) |
| **Renal insufficiency at the onset of the disease:** | |
| Renal insufficiency | 4 (14.8%) |
| Renal damage without insufficiency | 9 (33.3%) |
| Not involved | 14 (51.9%) |
| **Respiratory insufficiency at the onset of the disease:** | |
| Pulmonary insufficiency | 3 (11.1%) |
| Pulmonary damage without insufficiency | 15 (55.6%) |
| Not involved | 9 (33.3%) |
| **Other symptoms:** | |
| Arthralgias | 4 (14.8%) |
| Upper respiratory tract involvement | 16 (59.3%) |
| Gastrointestinal involvement | 1 (3.7%) |

BVAS – the Birmingham Vasculitis Activity Score, cANCA – antineutrophil cytoplasmic autoantibodies

Seven (25.9%) patients during the onset of the disease received only oral glucocorticoids and 20 (74.1%) patients took additional drugs (Table 2).

**Table 2.** Treatment during the first year of the disease

| | |
|---|---|
| AZA | 3 (11.1%) |
| PGT | 4 (14.8%) |
| CYC | 4 (14.8%) |
| CYC+AZA | 2 (7.4%) |
| AZA+PGT | 1 (3.7%) |
| CYC+PGT | 2 (7.4%) |
| CYC+AZA+PGT | 3 (11.1%) |
| CYC+MTX | 1 (3.7%) |

AZA – azathioprine, CYC – cyclophosphamide, PGT – pulse glucocorticoid therapy, MTX – methotrexate.

BVAS median was 7 (minimum (min) – 2; maximum (max) – 23). Age median was 52 years (min – 12; max – 75). Laboratory test results during the first visit are shown in Table 3.

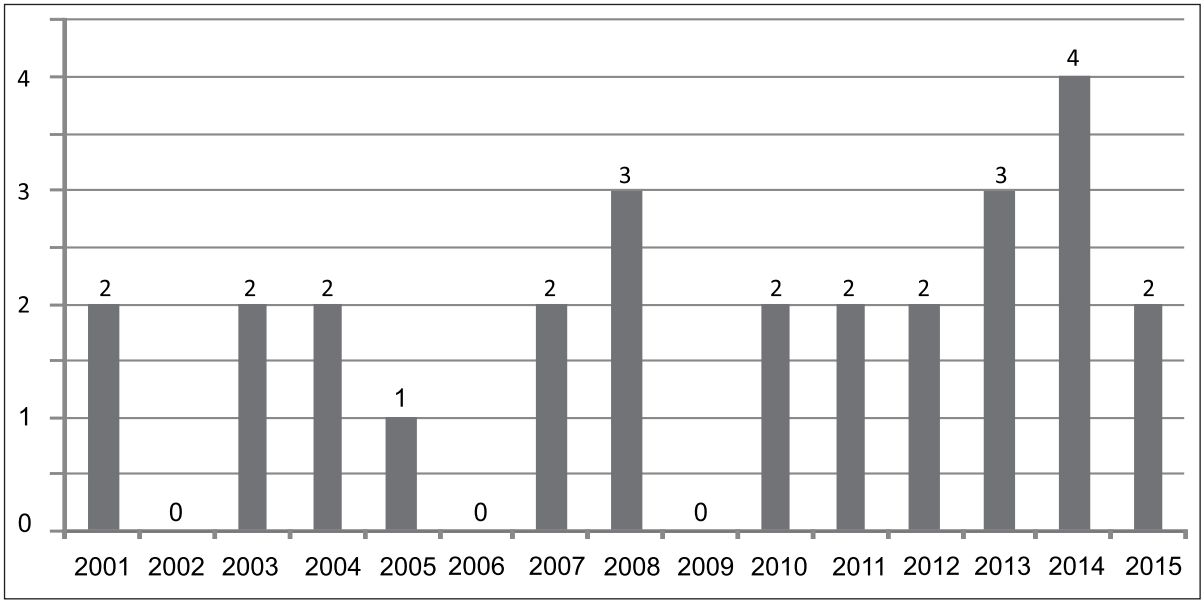


**Fig. 1.** Number of new cases each year at the Rheumatology Centre of Vilnius Santaros klinikos since 2001

**Table 3.** Laboratory test results during the first visit

| Test | Median | Minimum | Maximum |
|---|---|---|---|
| CRP | 20.5 | 0.3 | 172 |
| ESR | 43 | 3 | 120 |
| WBC | 8.42 | 4.57 | 26.3 |
| PLT | 296 | 108 | 702 |
| HB | 124 | 82 | 156 |
| Creatinine | 80 | 46 | 616 |

CRP – C reactive protein, ESR – erythrocyte sedimentation rate, WBC – white blood cell count, PLT – platelet count, B – haemoglobin level.

## DEATHS

During the observation time three female patients and two male patients died. One female patient died from mesenteric artery thrombosis, one from pneumonia, and one from complications of aortic coarctation. The overall mortality rate was 18.5% (5/27) during the 15-year follow-up. Both male patients died after profuse bleeding from the lungs. Four patients who had died were positive for *Staphylococcus aureus* and one result was missing. Moreover, three patients who recovered had a negative result and one result was missing as well. The median duration of the follow-up was 45.6 months (ranging from 2.9 to 154.6 months). The mean survival time was 126.6 months (95% confidence interval (CI) = 104.5 to 148.6) limited to 154.6 months for the longest-surviving patient (Fig. 2). We found statistically significant results comparing the BVAS groups. The median survival time for the BVAS group <10 was 144.5 months (95% CI = 125.7 to 163.3) whereas for the BVAS group ≥10 – 95.1 months (95% CI = 54.7 to 135.5) ($p$ = 0.024). However, the Cox regression analysis did not show any significant results.

## DISCUSSION

This cross-sectional study was mainly designed with the aim to assess possible prognostic factors at the onset of the disease and long-term survival differences of 27 AAV patients. Comparing this study with results from two tertiary Lithuanian centres published in 2010, the mean survival changed from 99.4 to 126.6 months (12). Moreover, the overall mortality rate decreased from 25.7% to 18.5% (12). Cumulative survival in our study at one and five years were 93% and 86%, respectively. Our results are comparable with other studies that reported a survival of 82% to 97% at one year, and 45% to 91% at five years for patients with MPA and GPA (13). However, a comparison of our results with data published in 2010 shows that cumulative survival at one and five years increased from 89% and

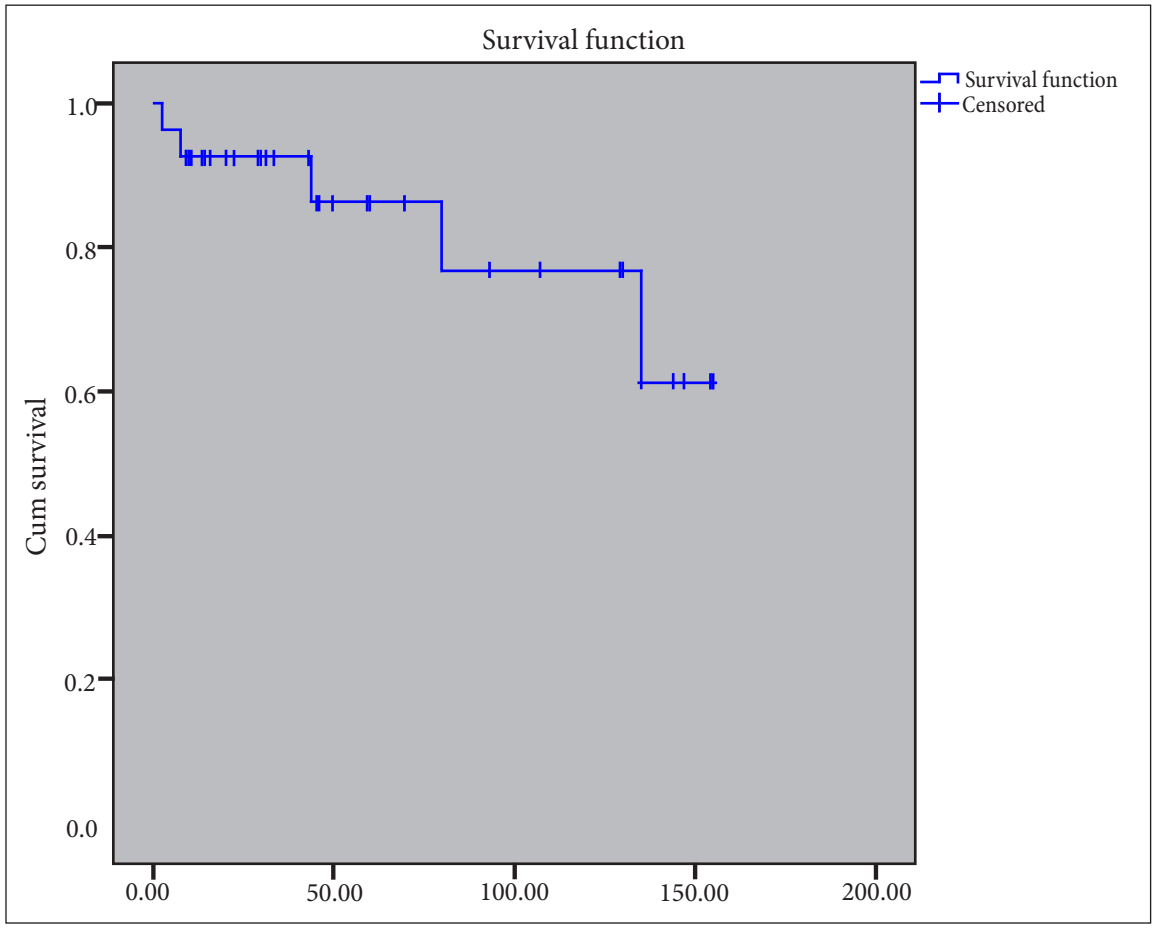


**Fig. 2.** The Kaplan-Meier analysis of survival, in months

67%, respectively, and this indicates extention of AAV patients' life expectancy during past 15 years in Lithuania. According to Flossmann et al., patients in the first year were most likely to die either of infection (48%) or of active vasculitis (19%), whereas patients after the first year died from the cardiovascular disease (26%), a malignancy (22%), or infection (20%) (11). Moreover, a higher mortality rate was associated with severe renal impairment, advanced age, or a low haemoglobin level (11). However, we did not find any significant differences in our study in these groups, most probably due to the small sample size limited to 27 AAV patients. A higher BVAS score at the onset of the disease was a bad prognostic factor and statistically significant in Kaplan-Meier analysis. However, we did not obtain any other significant results related to mortality predictors and therefore more clinical observational studies have to be conducted. Moreover, it is still not known whether an extremely active disease or active immunosuppressive therapy may be the main cause of death (11). Furthermore, according to Finkielman et al., a higher BVAS is associated with more frequently detectable ANCA (14), although we did not find any differences in our study. Comparing lung involvement, our results are nearly the same as described in the literature, for example, in a Chinese study the lungs were involved in 69.2% of all cases and in our study in 66.7% of all cases (15). However, kidney involvement was defined in 48.1% of all cases in our study compared with around 20% described in the literature (12, 16). Moreover, our study was limited to five organ systems while AAV can involve any organ, such as orbital structures or genitals (7, 8). We noticed a possible connection between the growth of *Staphylococcus aureus* from the nasopharynx and mortality, because results were positive for four out of five patients who died and negative for three out of four patients who recovered. Unfortunately, data for one patient who died and for one recovered patient were missing and therefore we did not obtain results supporting our hypothesis. However, the link between infections and the onset of AAV and the decrease in relapses after antibiotics was described by other authors (4). What is more, we were unable to find any relevant trials on AAV in which the term "recovered patient" was used. Usually the terms "long time remission", "remission maintenance", or "complete remission" were used and patients were not divided into categories. However, according to our experience we suggest that the term "recovered patient" might be useful to describe those who remained in a stable health condition for more than a year without glucocorticoids and immunosuppressants. Probably, a further discussion on this matter is needed.

## CONCLUSIONS

1. During the past 15 years, life expectancy for AAV patients increased from 99.4 to 126.6 months.

2. A high BVAS score at the onset of the disease is a bad prognostic factor related to a shorter life expectancy.

3. The growth of *Staphylococcus aureus* from the nasopharynx might be associated with higher mortality rates and relapses in AAV patients.

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## KLINIKINĖS CHARAKTERISTIKOS IR IŠGYVENAMUMO SKIRTUMAI ANCA ASOCIJUOTŲ VASKULITŲ GRUPĖJE: 27 PACIENTŲ SKERSPJŪVIO STUDIJA

*Santrauka*

**Tikslas.** Tyrimo tikslas buvo įvertinti ilgalaikį išgyvenamumą ir galimus prognostinius veiksnius ligonių, sergančių mikroskopiniu poliangitu ir granulomatoze su poliangitu bei hospitalizuotų į tretinio lygio Reumatologijos centrą Vilniuje.

**Tyrimo metodai.** Tai skerspjūvio studija, atlikta tiriant 27 ligonius, kurie buvo hospitalizuoti Vilniaus universiteto ligoninėje Santariškių klinikose nuo 2001 m. sausio 1 d. iki 2015 m. gruodžio 31 d. Surinkti ligonių demografiniai, klinikiniai, laboratoriniai, BVAS (Birmingham Vasculitis Activity Score) duomenys.

**Rezultatai.** Septyni (25,9 %) ligoniai ligos pradžioje gydyti tik geriamaisiais gliukokortikosteroidais, o likę 20 (74,1 %) gavo papildomą imunosupresinį gydymą. BVAS mediana buvo 7 (mažiausia – 2; daugiausia – 23). Visos kohortos amžiaus mediana – 52 metai (mažiausia – 12; daugiausia – 75). Bendras mirštamumas 18,5 %. Visos kohortos išgyvenamumo vidurkis 126,6 mėnesiai (95 % pasikliautinasis intervalas = 104,5 iki 148,6). Ilgiausiai tyrimo metu išgyvenęs ligonis – 154,6 mėnesiai.

**Išvados.** Ligonių išgyvenamumas per pastaruosius 15 metų AAV ligonių grupėje prailgėjo nuo 99,4 iki 126,6 mėnesių. Aukštas BVAS rezultatas ligos pradžioje yra blogas prognostinis veiksnys, susijęs su trumpesniu išgyvenamumu. *Staphylococcus aureus* augimas iš nosiaryklės gali būti susijęs su aukštesniu mirtingumo lygiu bei recidyvu AAV ligonių grupėje.

**Raktažodžiai:** ANCA-asocijuotas vaskulitas, baigtys, mikroskopinis poliangitas, granulomatozė su poliangitu, BVAS, išgyvenamumas