

## Clinical characteristics and long-term outcomes of 35 patients with Wegener's granulomatosis followed up at two rheumatology centers in Lithuania

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**Key words:** vasculitides; Wegener's granulomatosis; survival.

**Summary.** *Objective.* The aim of this study was to investigate the survival of Lithuanian patients with Wegener's granulomatosis, who were followed up at two tertiary rheumatology centers, and to find the factors possibly influencing the outcomes of this disease.

*Material and methods.* Thirty-five patients were followed up prospectively from the onset of disease (the first patient was enrolled in 1994) at Vilnius University Hospital and the Center of Rheumatology of Kaunas University of Medicine (17 and 18 patients, respectively). All patients in both the centers were followed up on a routine basis, and their records contained necessary information about laboratory and biopsy data; the censoring date (end of follow-up) was stated in June 2006.

*Results.* Among the patients, the most frequent organs involved were ear, nose, throat (ENT) (82.6%), lungs (74.3%), and kidney (renal involvement was defined by proteinuria/abnormal urine sediment) (45.7%). Renal insufficiency was present in 20.6% of all the patients. At the end of the study, 32.4% of patients had simultaneously all three organ systems involved, namely upper respiratory tract, pulmonary, and renal. ANCA positivity was found for 26 (74.3%) of all the patients. Overall mortality rate was 25.7% (9/35). The mean survival was 99.4 months (95% CI, 73.6; 125.3) limited to 149 months for the longest-surviving patient.

*Conclusions.* Female gender and all three specific organ involvements being present at the same time and higher vasculitis damage index were associated with poor outcome. Overall mortality rate was 25.7% (9/35) during the 12-year follow-up, and it is similar to the data from other European countries.

### Introduction

Wegener's granulomatosis (WG) is a unique clinicopathological disease entity characterized by necrotizing granulomatous vasculitis of the upper and lower respiratory tract, pauci-immune segmental necrotizing glomerulonephritis, and small-vessel vasculitis. It can be associated with significant morbidity and mortality. The incidence of the disease has increase from 5.2 to 12.0 cases per million in Scandinavian countries during the last 10 years, but this disease is still rare in the Baltic countries (2.1 cases per million) (1, 2). The survival of WG patients and prognosis did not change markedly over the 20-year period (3). Better diagnostics, and decrease of diagnostic delay, in addition to interdisciplinary approach to vasculitis problem, and new available treatment modalities may partially explain the changes in epidemiological data of this still enigmatic disease (4). The aim of this study was to investigate the survival of Lithuanian WG patients from two tertiary rheumatology centers and to find

the factors possibly influencing the outcomes of this disease.

### Patients and methods

Thirty-five patients were followed up from the onset of disease (the first patient was enrolled in 1994) at Vilnius University Hospital and Center of Rheumatology of Kaunas University of Medicine (17 and 18 patients, respectively). All patients fulfilled two or more of the ACR (1990) classification criteria for WG out of four possible, and all of them had biopsy proven granulomatous inflammation. All patients in both the centers were followed up on a routine basis, and their records contained necessary information about laboratory and biopsy data. For the patients surviving, the censoring date (end of follow-up) was stated in June 2006. At the end of follow-up, the vasculitis damage index (VDI) was recorded taking in account the involvement of 10 organ systems. For patients who did not survive, VDI was recorded by reviewing the patient's records

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or interviewing the last care-taking physician. The Pearson's chi-square test and Mann Whitney *U* were used to discriminate between the groups of different outcomes. Survival time and rate were assessed using Kaplan-Meier estimator, and logistic regression was used to predict poor outcome of the disease.

## Results

The mean age of 25 males and 10 females at the time of the diagnosis was 48.45±18.9 years in two clinical centers. The principal data referring to the time of the end of the study are summarized in Table 1. Among these patients, the most frequent organs involved were ear, nose, throat (ENT) (82.6%), lungs (74.3%), kidney (renal involvement was defined by proteinuria/abnormal urine sediment) (45.7%); general sickness was reported by 79.4% of patients. Renal insufficiency was less common but still documented in 20.6% of all the patients. It is noteworthy that 32.4% of patients had simultaneously all three organ systems involved at the end of the study, namely ENT, pulmonary, and renal. Antineutrophil cytoplasmic antibodies (ANCA) were detected in 26 (74.3%) patients; out of them, 19

had cANCA, while the remaining had pANCA or undifferentiated ANCA. The mean VDI score was 6.2±4.3 at the end of the study. Overall mortality rate was 25.7% (9/35) during the 12-year follow-up. The mean survival was 99.4 months (95% CI, 73.6; 125.3) limited to 149 months for the longest-surviving patient; 89%, 72%, 67% of the patients survived the first, second, and fifth year, respectively. The causes of death in nine patients are listed in Table 2. Six of them died because of sepsis or pulmonary bacterial infection, which was the direct cause of their death. The median of disease duration for those who did not survive was 16 months with a range of 1 to 97 months.

The univariate statistics showed that female gender and all three specific organ involvement, including ENT, pulmonary, and renal damage were prevalent in the group of patients with poor outcome; however, taken separately, they had no association with the outcome. Not surprisingly, higher VDI score was also noted in the group with poor outcome while age at the diagnosis had no relation to it (Table 3). Taking in account that the analyzed sample was rather small, the statistical significance of relation between the outcome and those three independent variables (female gender, higher VDI, and simultaneous damage of three organ system) was an important finding in this study. However, none of the above-mentioned variables had a significant influence on outcome in logistic regression model when analyzed together (data not shown).

The figure shows the survival rate of the patients discriminated by renal damage. Although no significant difference was found between those two Kaplan-Meier survival curves ( $P=0.3788$ ), it may be clearly seen that up to the 24th month of disease, the survival approximately retained the same in both groups with or without renal damage. The survival rate roughly diverted from the point of 24th month when it clearly diminished to 31% in the group with renal damage and retained as high as 73% in the group without renal damage at the end of this study.

Table 1. Main demographic, clinical, and immunological data of 35 patients with Wegener's granulomatosis at diagnosis

Characteristic	Value
Age at diagnosis, mean (SD), years	48.85 (18.9)
Gender: male/female	25/10
General symptoms: fatigue, fever, arthralgias, n (%)	27 (79.4)
Cutaneous involvement, n (%)	13 (38.2)
Mucous membranes (eyes), n (%)	10 (29.4)
ENT involvement, n (%)	28 (82.4)
Pulmonary involvement, n (%)	26 (76.5)
Cardiovascular, n (%)	–
Gastrointestinal, n (%)	–
Insufficiency of renal function, n (%)	7 (20.6)
Renal damage, n (%)	16 (47.1)
Neuropsychiatric, n (%)	5 (14.7)
ENT, pulmonary involvement and renal damage, n (%)	11 (32.4)
Other malignancies, diabetes, n (%)	8 (22.9)
Vasculitis damage index (VDI), mean (SD), score	6.2±4.3
ANCA positivity, n (%)	26 (74.3)

Table 2. Causes of death of 9 patients with Wegener's granulomatosis

Patient	Months after diagnosis	Cause of death
1	97	Congestive heart failure and probable pulmonary thrombembolia
2	12	Alveolar hemorrhage
3	24	Pancreas malignancy and cachexia
4	24	Sepsis, septic pneumonia, and alveolar hemorrhage
5	35	Sepsis, septic pneumonia, and septic shock
6	1	Acute renal failure, bacterial pneumonia
7	12	Bacterial pneumonia and septic shock
8	16	Sepsis
9	16	Sepsis

Table 3. The association between the outcomes and independent variables and of 35 patients with Wegener's granulomatosis in univariate statistics

Characteristic	Surviving patients N=26	Not surviving patients N=9	P
Age at diagnosis, mean (SD), years	45.6±20.0	50.4±15.8	0.510
Female gender, n (%)	5 (19.2)	5 (55.6)	0.038
Vasculitis damage index, mean (SD), score	5.3±3.9	8.9±4.4	0.030
Renal damage, n (%)	10 (40.0)	6 (66.7)	0.169
ANCA positivity, n (%)	18 (69.2)	8 (88.9)	0.245
ENT, pulmonary, and renal damage, n (%)	5 (20.0)	6 (66.7)	0.037

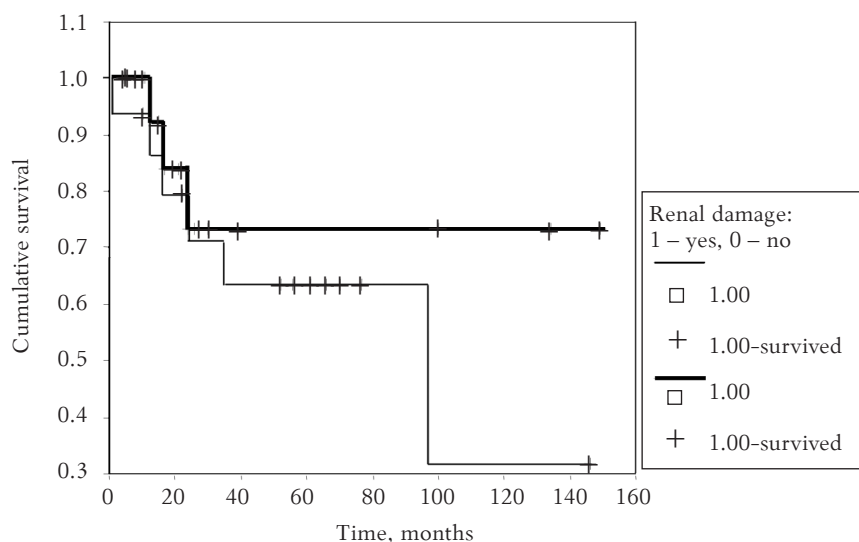


Fig. Survival of 35 patients with Wegener's granulomatosis discriminated by renal damage

## Discussion

This prospective study was carried in two tertiary centers with the aim to assess the overall survival rate and to predict factors possibly influencing the dichotomous outcomes of 35 WG patients. It is noteworthy to mention that this study mostly relied on the documents close to censoring data rather initial data, and the follow-up of those patients from the onset of disease carried more practical than scientific purposes. This study design was chosen because at the time, when the first patients entered the study in 1994, no valid instruments for the evaluation of disease activity or damage were available, and VDI designed in 2003 was applicable only at the end of this study. Majority (89%) of the patients survived the first year of follow-up from the diagnosis. During the 12-year study, of the 35 patients, 9 (25.7%) died, and the mean survival was 99.4 months. The recent studies from Poland (5), Norway (6), Turkey (7), Germany (8), and United Kingdom (9) showed overall mortality rate similar to our findings, which ranged from 27.2 to 37%, and 5-year survival rate of 60–80% depending on renal function. The only study from Turkey reported about 41% overall mortality rate and lower mean survival being 59% at three years after diagnosis (10). The researchers from neighboring Poland in a prospective cohort

of 60 patients demonstrated that 88% of WG patients survived the first year of follow-up from diagnosis while 84% remained alive after the second year of observation, and this corresponds to our data, although survival in Polish cohort was shorter if compared to Lithuanian cohort (67.1 versus 99.4 months) (5). Both the Norwegian (6) and UK (9) studies demonstrated five-year survival higher than 75% while the best survival time was showed by German study indicating a median survival of 21.7 years and better outcome (8). One German study (8) and study from Finland (4) pointed out to the necessity of interdisciplinary approach to the care of the patients with suspected vasculitis, which results in reduced diagnostic delay. The duration of the symptoms before the start of the treatment was mentioned to be from 4 to 6 months in Norway study (6), and it was the shortest period ever found in the literature on WG. Our study, carrying mostly a retrospective pattern, did not document characteristics of the first symptoms, but an interdisciplinary approach to patients' follow-up was very important as a substantial part of patients were referred to a rheumatologist by ENT specialists, and upper respiratory tract involvement prevailed in the clinical picture of these patients. Interestingly, the damage of the ENT system is described as having a protective

role in two independent studies (7, 11), and patients with ENT granulomatous inflammation achieve better outcome than those without. These findings could indicate that the prognosis of WG might be governed by the balance between the granulomatosis as opposed to the vasculitic disease process (11). It is generally accepted and no longer argued that WG patients of older age, with renal involvement and infection have worse outcomes and higher mortality rates (7, 8, 11–13). In our study, the infection was the most frequent cause of the death. It can be debated that to find the balance between the immunosuppression ultimately needed in the treatment of WG and the risk of bacterial infection evolving in these cases are the most complicated issue in managing the WG patients. This assumption goes along with the study by Harper and Savage, which highlights the needs for less toxic treatment regimens (13). For treatment issues, the researchers' opinions often contradict each other. According to Koldingnes and Nossent (14), relapses were associated with less intensive initial treatment in terms of lower cyclophosphamide dose and shorter time taking prednisone. Conversely, the study by Gottenberg et al. (12) showed that the initial route of cyclophosphamide administration appeared to have no effect on survival. Again, our study had no power to highlight the treatment influence on the outcome hoping to analyze it in future studies on vasculitis. In univariate statistics of this study, gender, particularly fe-

male gender, higher VDI, and simultaneous organ involvement were found to be significantly related to the outcome. In addition, we found differences in survival of the patients regarding renal function though it did not reach the statistical significance. Differently from survival analysis, none of predictors including renal function predicted the outcome of these patients in logistic regression. Small sample size may partially explain the lack of the predictors and the contradictions to other studies, where renal damage was found to be the strongest predictor of poor outcome (5, 6, 8, 10, 12, 13).

### Conclusions

1. The univariate statistics showed that female gender and all three specific organ involvement being present at the same time, and higher vasculitis damage index were associated with poor outcome although logistic regression analysis did not confirm it.

2. Bacterial infection was the most common direct cause of the death in the cohort of the patients with poor outcome. Of the 9 patients, 6 died because of sepsis or pulmonary bacterial complications.

3. Overall mortality rate was 25.7% (9/35) during the 12-year follow-up. The mean survival was 99.4 months; 89%, 72%, 67% of the patients survived the first, second, and fifth year, respectively. These findings are comparable to the data obtained from other European countries.

## Lietuvos reumatologijos centruose stebėtų 35 sergančiųjų Wegenerio granulomatoze klinikinė charakteristika ir baigtys

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**Raktažodžiai:** vaskulitai, Wegenerio granulomatozė, išgyvenamumas.

**Santrauka.** *Tyrimo tikslas.* Ištirti pacientų, stebėtų dviejuose trečiojo lygio reumatologijos centruose ir sergančių Wegenerio granulomatoze, išgyvenamumą ir nustatyti galimai jiems įtakos turinčius veiksnius.

*Tyrimo medžiaga ir metodai.* 35 pacientai gydyti ir stebėti nuo ligos pradžios (pirmas pacientas įtrauktas į tyrimą 1994 m.). Vilniaus universiteto ligoninės (17 pacientų) ir Kauno medicinos universiteto klinikų Reumatologijos centre (18 pacientų). Pacientai buvo stebimi vadovaujantis įprastinės klinikinės reumatologinės praktikos schemomis iki 2006 m. liepos mėn.

*Rezultatai.* Įvertinus kliniškai, nustatyta, kad šiems pacientams vyravo viršutinių kvėpavimo takų pažeidimas (82,6 proc.), plaučių pažeidimas (74,3 proc.) ir inkstų pažeidimas (45,7 proc.). Inkstų funkcijos nepakankamumas nustatytas 20,6 proc. visų pacientų. Tyrimo pabaigoje konstatuota, kad vienu metu viršutinių ir apatinių kvėpavimo takų ir inkstų pažeidimas buvo 32,4 proc. pacientų. ANCA rasta 26 (74,3 proc.). Mirštamumas – 25,7 proc. (9/35). Vidutinis išgyvenamumas – 99,4 mėn. (95 proc. PI 73,6; 125,3), ilgiausiai išgyvenęs pacientas – 149 mėn.

*Išvados.* Moteriškoji lytis, trijų organų pažeidimas vienu metu (viršutinių ir apatinių kvėpavimo takų ir inkstų) ir didesnis pažeidimo indeksas buvo susiję su bloga ligos baigtimi. Mirštamumas buvo 25,7 proc. (9/35) per 12 stebėjimo metų ir jis nesiskiria nuo kitų Europos šalių analogiškų duomenų.

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