The epidemiology of primary systemic vasculitides involving small vessels in Crete (southern Greece): a comparison of older versus younger adult patients

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Abstract

Background

The frequency of primary systemic small vessel vasculitides (PSV) varies among different geographic regions and age categories. We studied PSV in patients from middle-eastern Crete (Greece), and compared clinical characteristics in younger (<65 years) versus older (≥65 years) adult patients.

Methods

The records of 67 patients (33 younger, 34 older adults) diagnosed with PSV during 1995–2003 who were referred to a mixed secondary/tertiary care University Hospital in Crete were reviewed. Data on clinical manifestations, diagnosis, therapy, and adverse outcomes (end stage renal disease, death) during a median follow-up of 6 (range 0-12) years were recorded. Multivariate regression analysis was applied to identify independent predictors for adverse outcomes.

Results

The overall annual incidence of PSV was 19.5/million (95% confidence interval [CI] 15.7-23.4), 48.9/million (95% CI 33.8–63.9) in older and 12.4/million (95% CI 7.7-17) in younger adults. Microscopic polyangiitis was more prevalent in older patients (65%) and Wegener's Granulomatosis in younger patients (52%). Thirty-one percent of older patients developed end-stage renal disease as compared to 11% of younger patients (p=0.103). Mortality rates were 60% in older patients and 19% in younger patients (p=0.001). In multivariate regression analysis age (β=0.33 per 1-year, p=0.005), serum creatinine (β=0.29 per 1-mg/dL, p=0.011), and lung involvement (β=0.36, p=0.002) at the time of diagnosis were independent predictors for end stage renal disease and/or death.

Conclusions

This study documents increased frequency and significant mortality of PSV among older people in Crete, with MPA being the most prevalent type. Age, serum creatinine, and lung involvement are important predictors for adverse outcome in these patients.

Key words

Microscopic polyangiitis, Wegener's granulomatosis, Henoch-Schönlein purpura, ANCA-associated vasculitis.

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Introduction

Primary systemic small vessel vasculitides (PSV) are characterized by systemic inflammation of the small vessels. The term primary denotes that there is no secondary cause (*e.g.* virus infection) identified responsible for the inflammatory process. Although rare, PSV are associated with high morbidity and mortality rates and their diagnosis and management can be challenging. PSV include microscopic polyangiitis (MPA), Wegener's granulomatosis (WG), Churg-Strauss syndrome (CSS), Henoch-Schönlein purpura (HSP), essential cryoglobulinemic vasculitis, and cutaneous leukocytoclastic angiitis, as defined in the Chapel Hill Consensus Conference (CHCC) nomenclature (1). CSS, WG, hypersensitivity vasculitis, and HSP were also classified by the American College of Rheumatology (ACR), while MPA was not separated from polyatreriitis nodosa (2). Recently, the term "antineutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV)" has been introduced by the European Vasculitis Study Group (3). PSV annual incidence varies in different geographic regions across the world. Older patients have rarely been included in PSV clinical trials; therefore the clinical characteristics, the response to therapy, and the outcome are less well defined in this age group (3). We undertook a study to determine the annual incidence of PSV, namely MPA, WG, CSS, unclassified AAV (UCAAV), and HSP, in the middle-eastern part of Crete, a geographically isolated and genetically homogenous island in Southern Europe. Herein we report on age distribution of PSV and age differences in clinical characteristics, therapies, adverse outcome, such as end stage renal disease (ESRD) and death, and predictors of these outcomes.

Patients and methods

Study population

Patients were diagnosed and/or followed by the Departments of Internal Medicine, Nephrology, and Rheumatology of the University Hospital of Heraklion, a mixed secondary and tertiary hospital, which serves as the only referral centre for systemic vasculitis in Crete. Patients with suspected systemic vasculitis were either referred to the hospital by general practitioners and regional hospitals or they presented to the emergency department of the hospital. Between January 1, 1995 and December 31, 2003 all newly diagnosed adult (>14 years old) patients with PSV were registered. The cut-off value of 14 years was used because in the Greek National Health System persons above this age are referred to adult physicians.

Inclusion criteria

A definite diagnosis of MPA, WG, CSS, HSP, or UCAAV was required. The diagnosis was denoted in the medical records and confirmed or revised by two independent investigators (SCP, GSP). ACR criteria were used for the classification of patients with WG, CSS and HSP (1). The CHCC definitions were applied to distinguish patients with MPA (2). Under the term UCAAV we denoted those cases of AAV defined according to the European League Against Rheumatism (EULAR) recommendations (3), for which a definite diagnosis of either MPA or WG or CSS was not possible.

Exclusion criteria

Patients with secondary vasculitides (*e.g.* associated with other inflammatory diseases, including hepatitis-associated vasculitis) were excluded. All leucocytoclastic vasculitides were excluded because they were not usually referred to the University Hospital of Heraklion and thus, their incidence would be underestimated. Cases with essential cryoglobulinemic vasculitis were also excluded, considered as secondary vasculitis.

Definitions

Organ system (*e.g.* renal, lung, skin, musculoskeletal, gastrointestinal) involvement was considered only if the manifestations were due to vasculitis. Lung involvement was defined by the presence of at least one of the following: (i) cough, (ii) respiratory distress, (iii) haemoptysis (iv) abnormal chest x-ray (solitary or multiple nodules and masses, bilateral alveolar infiltrates combined with a falling haemoglobin level), (v) abnormal chest or high

resolution computer tomography (*e.g.* ground glass opacities, cavitated nodules/masses), (vi) increased values of the diffusing capacity for carbon monoxide (DLCO), (vii) diagnostic tissue biopsy (4). Renal involvement was considered if at least one of the following was noted: (i) a serum creatinine (SCr) value >1.4 mg/dL, (ii) active urine sediment (≥5 red blood cells per high-power field and/or cellular casts), (iii) proteinuria (24-hour urine protein excretion >200mg or spot urine protein/creatinine >0.2) (5). Renal function was assessed by SCr value; SCr <1.4 mg/dl indicating normal renal function; SCr 1.4-3 mg/dL indicating moderate renal damage; SCr >3 mg/dL indicating severe renal damage. Gastrointestinal involvement was considered as: (i) vomiting, or (ii) abdominal pain, or (iii) abnormal liver enzymes, or (iv) melena/haematochezia. Skin involvement included: (i) skin ulcers, or (ii) plaques, or (iii) nodules, or (iv) purpuric rush. Musculoskeletal involvement was defined as the presence of: (i) arthralgias, or (ii) arthritis, or (iii) myalgias. Anaemia was defined as Hb <12g/dL. High erythrocyte sedimentation rate (ESR) was considered when >80mm/h. Induction therapy denoted the initial aggressive immunosuppressive treatment intended to achieve remission. We defined as younger adults the patients aged <65 years, and as older adults those aged ≥65 years (6).

Data collection

Data were collected retrospectively from the medical records and patients or their families were contacted by phone by one of us (SHP) to determine their status by July 2007. Incidence rates were calculated based on the population statistics dated January 1, 2001 (provided by the Greek Institute of National Statistics). The adult population in middle-eastern Crete was 369,428 (men 184,522; women 184,906) and the population aged ≥65 years was 72,767 (men 33,066; women 39,701). This population has been relatively stable with minimal migration during the past two decades. Both cytoplasmic ANCA (c-ANCA) and perinuclear ANCA (*p*-ANCA) were tested using indirect immunofluorescence.

Ethical issues

The protocol was approved by the Research Ethics Committee of the University Hospital of Heraklion, Crete.

Statistical analysis

The Fisher's exact test for categorical data and the Mann-Whitney test for numerical data were used to examine for differences between younger and older adult patients. Annual incidence rates for the years 1995-2003 were reported as the number of newly diagnosed cases per 1 million inhabitants for all cases per year. They were calculated using the number of new cases divided by the estimated population of the respective age. The mean (95% confidence interval [95% CI]) incidence was then calculated separately for each age group. To determine predictors for ESRD and/or death multivariate linear regression analysis was performed using demographic and clinical characteristics as independent variables. Kaplan-Meier survival plots were generated and log rank statistics were performed. *P*-values (two-tailed) <0.05 were considered as statistically significant. The Statistical Package for Social Sciences (SPSS, Inc.) version 13.0 was used for all analyses.

Results

General characteristics and incidence of PSV

Sixty-seven (67) patients were included in the study. The demographic and clinical characteristics of the patients are shown in Table I. Thirty-three patients (49%) were <65 years old, and 34 patients (51%) were ≥65 years old. The mean ± standard deviation follow up time was 5.8±3.3 years (median 6 years, range <6 months-12 years). Twenty-six patients were classified as MPA, 21 as WG, 8 as HSP, and 12 as UCAAV. Kidney biopsies were performed in 42 patients (63%) and reported pauci-immune glomerulonephritis (82% of cases), crescenting glomerulonephritis (63%), necrotizing glomerulonephritis (61%), and chronic glomerulonephritis (21%). Kidney biopsy-proven were 18 cases with MPA, 14 cases with WG, 2 cases with HSP, and 8 cases with UCAAV. MPA was more prevalent in older patients [65% *vs.* 12%, $p<0.001$], whereas WG was more frequent in younger patients (52% *vs.* 12%, $p=0.001$) (Table I). A similar frequency of UCAAV (21% *vs.* 15%) and HSP (15% *vs.* 9%) was found in younger and older patients. The annual incidence of each PSV type is shown in Table II. The overall annual incidence of PSV in adult population was 19.5/million; incidence was higher in older (48.9/million) than in younger adults (12.4/million).

Clinical characteristics of AAV – Age category and organ/system involvement

Lung involvement occurred significantly more often in older patients with AAV (90% *vs.* 61%, $p=0.013$) (Table III). Radiographic findings suggestive of PSV were found in 42 (25 older) patients. Twenty (13 older) patients had pulmonary haemorrhage. A similar frequency of anaemia, high ESR, gastrointestinal,

Table I. Characteristics of patients diagnosed with PSV according to age group.

	Age at diagnosis		
	<65 years	≥65 years	*p*-value[1]
No. patients	33	34	
Gender			
Females (n, %)	19 (58)	20 (59)	0.918
Males (n, %)	14 (42)	14 (41)	
Type of PSSV			
MPA (n, %)	4 (12)	22 (65)	<0.001
WG (n, %)	17 (52)	4 (12)	0.001
UCAAV (n, %)	7 (21)	5 (15)	0.539
HSP (n, %)	5 (15)	3 (9)	0.476

[1]Fisher's exact test.

Table II. Adjusted incidence rates of PSV according to age group in an adult Crete population.

Vasculitis	Age group		
	Total	<65 years	≥65 years
All PSV	19.5 (15.7–23.4)	12.4 (7.7–17.0)	48.9 (33.8–63.9)
MPA	10.2 (5.8–14.6)	3.4 (1.1–5.6)	38.2 (21.7–54.7)
WG	6.6 (3.7–9.6)	6.7 (4.2–9.3)	6.1 (-1.6–13.8)
HSP	2.4 (0.0–4.8)	0.7 (-0.4–1.9)	9.2 (0.0–18.3)
UCAAV	4.8 (1.4–8.2)	3.5 (0.7–7.0)	9.2 (0.0–18.3)

[1] Data are presented as mean (95% confidence interval).

Table III. Clinical characteristics of AAV cases according to age group.

	Age at .diagnosis		
	<65 years	≥65years	*p*-value[1]
No. patients	28	31	
Organ involvement			
Lung involvement (n, %)	17 (61)	28 (90)	0.013
Renal involvement			
Abnormal urine sediment (n, %)	23 (85)	29 (94)	0.402
Serum creatinine (mg/dL) (mean ± SD)[2]	3.1 ± 2.9	4.2 ± 2.5	0.040
<1.4 mg/dL (n, %)	11 (41)	3 (11)	0.040
1.4–3.0 mg/dL (n, %)	5 (18)	9 (32)	
>3.0 mg/dL (n, %)	11 (41)	16 (57)	
Gastrointenstinal involvement (n, %)	10 (37)	9 (30)	0.589
Skin involvement (n, %)	11 (41)	11 (37)	0.791
Musculoskeletal involvement (n, %)	21 (78)	22 (73)	0.765
Anaemia (n, %)	25 (96)	25 (89)	0.612
ESR >80 mm/hr (n, %)	25 (100)	25 (93)	0.491
ANCA			
ANCA negative (n, %)	10 (37)	5 (18)	0.138
c-ANCA positive (n, %)	15 (56)	4 (14)	0.002
p-ANCA positive (n, %)	2 (7)	19 (68)	<0.001
Treatment[3]			
CY[4] (iv or orally) + CS[5] (iv or orally)	21 (84)	23 (82)	0.621
Pulses iv MP[6] + iv CY	15 (60)	20 (71)	
CY monotherapy	0 (0)	1 (4)	
CS + immunosuppressants other than CY	2 (8)	2 (7)	
CS monotherapy	2 (8)	1 (4)	
No treatment	0 (0)	1 (4)	
Outcome			
ESRD (n, %)	3 (11)	9 (31)	0.104
Death (n, %)	5 (19)	18 (60)	0.003
Within one year after diagnosis (n, %)	1 (20)	6 (33)	0.106
ESRD and/or death (n, %)	6 (21)	19 (61)	0.003

[1] Chi-squared test or Fisher's exact test for categorical data, Mann-Whitney test for numerical data. [2] Mean ± standard deviation; [3] Data were available for 53 patients; [4] Cyclophosphamide; [5] Corticosteroids; [6] Methylprednisolone.

skin, and musculoskeletal, involvement was found in younger and older patients. Renal involvement (determined by clinical and histological findings) was equally distributed between the two age groups, although SCr at diagnosis was significantly higher in older patients (4.2±2.5 mg/dL *vs.* 3.1±2.9 mg/dL, p=0.040). c-ANCA were more prevalent in younger patients (56% *vs.* 14%, p=0.002), whereas p-ANCA were more prevalent in older patients (68% *vs.* 7%, p<0.001). ANCA negative cases were found more frequently in the younger than in the older patient group (p=0.055).

– Age category and induction therapy

Information regarding the induction therapy was available for 53 patients. (Table III). Forty-four patients (83%) received combination of cyclophosphamide (CY) (intravenously or orally) with corticosteroids (CS). Thirty-five patients (20 older) received pulses of iv cyclophosphamide and iv methylprednisolone, five patients received iv cyclophosphamide with oral corticosteroids, and the remaining four patients received oral cyclophosphamide with oral corticosteroids. One older patient received only cyclophosphamide due to major depressive disorder. Four patients (8%) (2 older) were treated with other immunosuppressants combined with corticosteroids, three patients with corticosteroid monotherapy, and one older patient denied any therapy.

– Age category and development of ESRD or death

During follow-up, 10 patients (17%) with AAV developed ESRD while another two (3%) were already on ESRD at the time of diagnosis (Table III). Five patients had MPA, 5 had WG, and 2 had UCAAV. Six out of 10 patients (60%) developed ESRD within 3 months after diagnosis. Older patients showed a trend for more frequent development of ESRD compared to younger patients (31% *vs.* 11%, p=0.104). Ten out of 12 patients who developed ESRD (83%) died during follow up; 9 were older adults.

A total of 23 AAV patients (39%) died during follow up, 5 of them were aged <65 (19%) and 18 were ≥65 years (60%) (p=0.003) (Table III). Seven patients (30%) died within the first year after diagnosis. Six of them were aged ≥65 years, and died due to pulmonary haemorrhage [n=3 (n=2 on ESRD)], sepsis (n=2), and acute myocardial infarction (n=1). One younger patient died due to lung cancer. Sixteen patients (70%) died after the first year of diagnosis. Older patients (n=12) died due to pulmonary haemorrhage (n=1), Pneumocystis carinii pneumonia (n=1), fungal pneumonia (n=1), tuberculous pneumonia (n=1), pulmonary oedema (n=1), acute myocardial infarction (n=1), sepsis (n=2). Younger patients (n=4) died due to relapse of WG and pancreatitis (n=1), colon cancer with liver metastases (n=1), and sepsis (n=1). For the remaining 5 deaths there

Table IV. Predictors for adverse outcomes (ESRD, death) in AAV patients.

	ESRD		Death		ESRD and/or death		
	–	+	–	+	–	+	
Age ≥65 years	45.5%	75.0%	35.3%	78.3%**	35.3%	76.0%**	β=0.33 (p=0.005)[1]
Male gender	34.1%	41.7%	38.2%	30.4%	38.2%	32.0%	
ANCA							
p-ANCA	37.5%	41.7%	28.1%	57.1%*	28.1%	52.2%	
c-ANCA	37.5%	25.0%	34.4%	28.6%	40.6%	26.1%	
Organ involvement							
Anemia	90.0%	100.0%	93.5%	90.5%	93.5%	91.3%	
GI	31.0%	41.7%	36.4%	22.7%	36.4%	29.2%	
Musculoskeletal	76.2%	83.3%	75.8%	72.7%	75.8%	75.0%	
Skin	40.5%	41.7%	39.4%	36.4%	39.4%	37.5%	
Lung	70.5%	100.0%*	61.8%	100.0%**	58.8%	100.0%***	β=0.36 (p=0.002)
SCr ≥2.5mg/dL	52.4%	80.0%	43.8%	76.2%*	45.5%	77.3%*	β=0.29 (p=0.011)

*p<0.05, **p<0.01, ***p<0.001 (Fisher's exact test for comparing between patients who developed or not ESRD, death, death and/or ESRD).
[1] Standardized β correlation coefficient. Linear regression analysis using the composite outcome ESRD and/or death as dependent variable and age (per 1-year), lung involvement (dummy variable), and baseline SCr (per 1-mg/dL) as independent variables.

were no available data. The causes of death for patients who died on ESRD after the first year from diagnosis were pulmonary haemorrhage (n=1), pancreatitis (n=1), sepsis (n=3), pulmonary oedema (n=1), acute myocardial infraction (n=1), unknown cause (n=1).

– Predictors for adverse outcome in AAV

We next assessed the risk for developing ESRD and/or death in AAV patients according to various demographic and clinical characteristics (Table IV). Lung involvement was present in all 12 patients (100%) who developed ESRD, compared to 31 out of 44 patients (71%) who did not (p=0.049). Death was associated with age ≥65 years (78% *vs*. 35%, p=0.003), p-ANCA (57% *vs*. 28%, p=0.047), lung involvement (100% *vs*. 62%, p=0.001), and SCr ≥2.5mg/dL (76% *vs*. 44%, p=0.026) at diagnosis. Similarly, the composite end-point ESRD and/or death was associated with age ≥65 years (76% *vs*. 35%, p=0.003), lung involvement (100% *vs*. 59%, p<0.001), and SCr ≥2.5mg/dL (77% *vs*. 46%, p=0.026) at diagnosis. In multivariate regression analysis age (β=0.33, p=0.005), SCr (β=0.29, p=0.011), and lung involvement (β=0.36, p=0.002) at diagnosis were independent predictors for ESRD and/or death. Survival plots in AAV cases were created using age, SCr, lung involvement and ESRD at diagnosis as stratification factors (Fig. 1). Age ≥65 years (p=0.002), SCr ≥2.5 mg/dL (p=0.013), lung involvement (p=0.004), and development of ESRD (p=0.003) were associated with decreased survival.

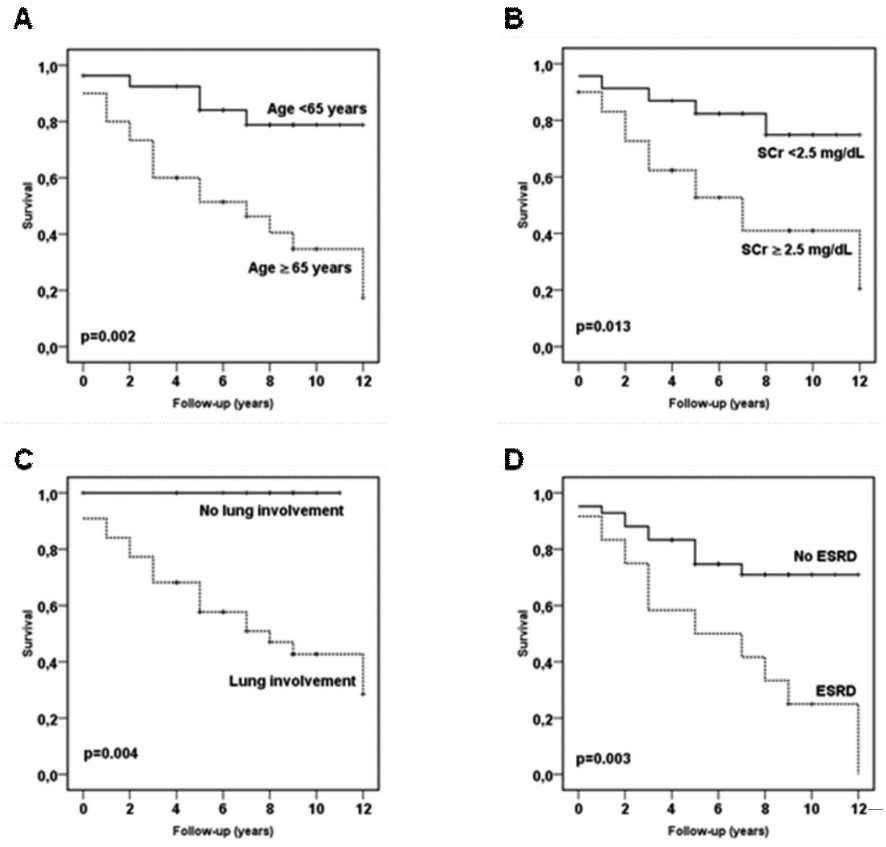

Fig. 1. Survival plots in AAV patients according to age, baseline serum creatinine, lung involvement, and development of ESRD.

Clinical characteristics of HSP

A total of 8 HSP cases were found; 5 in younger and 3 in older patients. Male sex was predominant (88%). Mean SCr at diagnosis was 1.0 mg/dL. None of the patients had lung involvement. Purpura and abnormal urine sediment was observed in seven patients (88%),

musculoskeletal involvement in five (63%), and GI involvement in four (50%). Renal biopsy was performed in two patients and exhibited proliferative glomerulonephritis with messangial IgA deposits. All cases were treated with corticosteroids and four patients received immunosuppressive therapy (azathioprine, methotrexate, cyclophosphamide) in addition. No patient developed ESRD and only one death occurred due to traumatic spleen rupture.

Discussion

PSV represent a group of diseases of the small vessels affecting various organs, mainly the kidneys and the lungs. Although considered rare, PSV are associated with significant morbidity and mortality (7) especially at the pre-immunosuppressive therapy period where the 1-year survival rate for WG was less than 20% (8). We found that the overall annual incidence of PSV among the adult population of middle-eastern Crete was 19.5/million. The incidence was higher in adults aged ≥65 years (48.9/million) than in adults <65 years old (12.4/million). A marked age-specific increase in the incidence of PSV has also been reported by Watts *et al*. in Norwich, UK (53/million in ages 65-74 years), by Gonzalez *et al*. in Lugo, Spain (34/million in ages 45-74 years) and by Fujimoto *et al*. in Miyazaki, Japan (44.8/million) (9-11).

The estimated annual incidence of PSV in middle-eastern Crete was 10.2/million for MPA, 6.6/million for WG, 4.8/million for UCAAV, and 2.4/million for HSP. MPA annual incidence in Norwich was reported at 8.4/million; in Lugo at 11.6/million; and in Miyazaki at 15/million (9, 11). A similar to our annual incidence of WG was reported in Norwich (11/million), whereas a lower incidence was found in Lugo (3/million) and in Miyazaki (no case) (9-11). The HSP incidence was reported equally low (1.2/million) by Watts *et al.,* who used the ACR classification criteria (12). Using the Michel *et al*. classification criteria, based on the same database collected by the 1990 ACR vasculitis subcommittee, the HSP incidence in Lugo, for population 21 years or older over the period 1988-1997, was 14.3/million (13). However, the HSP incidence in adults from Lugo would have been much lower (7.9/million) if it had been calculated using only the patients that fulfilled the CHCC definitions for HSP (14). No case of CSS was found in our cohort. The average annual incidence of CSS for adult population was 2.4/million in Norwich and 1.1/million in Lugo (12, 14).

In accordance with the findings from the European Vasculitis Study (EUVAS) Group (15), older patients exhibited significantly higher SCr levels at diagnosis compared to younger patients. Nevertheless, the percentage of individuals who reached ESRD did not differ between the two age groups. This could be due to comparable efficacy of treatment in the two groups, or to an end of life before reaching ESRD particularly in the older adults. We found lung involvement to be very common in MPA, WG and UCAAV, in agreement with the literature (4). In our series lungs were affected more frequently in the older compared to younger patients (p=0.007). In contrast, Hoganson *et al*. reported similar frequencies of lung involvement between the two age groups, but they used the 75 years as the threshold of older age (16).

We found a rate of ESRD in the first year of 9%. Rates of ESRD differ among different studies, ranging from 8% at 1 year to 24% at 3 years in a cohort of 37 older patients with PSV and renal involvement in Ljubljana (Slovenia), and up to 54% after 2 years in another cohort of 56 patients with PSV and renal involvement in Miyazaki (17, 18).

Our findings confirm the results from previous studies showing that age and renal function (SCr) are important predictors for ESRD and/or death in patients with AAV (19-22). In addition, we found lung involvement to be a strong independent prognostic factor in our cohort, as it was present in all patients who developed death and/or ESRD. In contrast, none of the patients who did not have lung involvement developed these outcomes (Table IV). Slot *et al*. reported that age >65 years and SCr >5.65 mg/dl at diagnosis were associated with elevated mortality in the first year (relative risk [RR] 6.5, 95% CI 1.6-13.7; RR 2.2, 95%CI 0.9-6.9, respectively) in patients with PR3-ANCA positive vasculitis and renal involvement (20). Accordingly, Bligny *et al*. reported age >52 years and SCr >1.8mg/dl to have a pejorative prognostic value (p<0.001 and p<0.002 respectively) according to univariate analysis among patients with WG. Multivariate analysis retained age >52 years as an independent predictor of poor outcome (hazard ratio [HR] =3.4, p=0.04) (21). Weidner *et al*. showed, in a cohort of patients with AAV, a 1.082-fold increase in risk per year of age, corresponding to a doubling in risk of death every 8.8 years. A 1.003-fold increase in risk per μmol/L of SCr in the first month was also corresponding to a doubling in risk of death in steps of 277 μmol/L SCr (22). On the contrary, Lane *et al*. found that age was a significant risk factor, but only to the same extent as in the reference population. When age was adjusted for, neither renal nor lung involvement was found associated with death (23). Reinhold-Keller *et al*. found age >50 years ([HR 5.5, 95% CI 2.0-15.0), kidney involvement with impaired renal function (HR 5.4, 95% CI 1.8-16.7), and lung involvement (HR 3.8, 95% CI 1.3-11.2) at diagnosis, to be significant predictors of survival among patients with WG (24). Uezono *et al*. showed that lung involvement and requirement of immediate dialysis therapy at diagnosis conferred poorer survival rates (HR, 3.3, 95% CI, 1.1–9.7; HR 2.7, 95% CI, 1.0-7.2, respectively) among patients with MPO-ANCA positive primary renal vasculitis (WG cases and CSS cases were not included) (18).

We found eight adult cases of HSP. Eighty eight percent of HSP patients had renal involvement but no one developed ESRD during the follow up period. In a cohort of 31 adult patients with HSP in Lugo, 45% of patients exhibited mild and severe renal manifestations and 7% reached ESRD after 5 years' median follow up (25).

There are several caveats in our study including the retrospective design and the absence of a unified protocol for therapy and follow-up. On the other hand, randomized controlled trials may exclude a significant percentage of patients and thus, generalization of their

data to a more real-life scenario can be challenging. Kidney biopsies were performed in a significant proportion of patients (63%) providing objective evidence for renal involvement.

In summary, this study documents the relative high incidence of PSV in older people in middle-eastern Crete. Although PSV represents a rare group of diseases, nonetheless, it is associated with significant morbidity (renal and lung involvement) and mortality in older patients. MPA was the prevalent PSV type among the older and WG among the younger patients. Age, SCr and lung involvement at diagnosis were significant independent predictors for death in this population. Our data suggest that efforts to improve the outcomes in these patients need to be directed also at co-morbidities.

References

1. LIGHTFOOT RW JR, MICHEL BA, BLOCH DA *et al*.: The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. *Arthritis Rheum* 1990; 33: 1088-93.
2. JENNETTE JC, FALK RJ, ANDRASSY K *et al*.: Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum* 1994; 37: 187-92.
3. HELLMICH B, FLOSSMANN O, GROSS WL *et al*.: EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis. *Ann Rheum Dis* 2007; 66: 605-17.
4. MANGANELLI, FIETTA P, CAROTTA M, PESCI A, SALAFFI F: Respiratory system involvement in systemic vasculitides. C*lin Exp Rheumatol* 2006; 24 (Suppl. 41): S48-59.
5. ADLER S, FAIRLEY K: The Patient with Haematuria or Proteinuria, or Both, and Abnormal Findings on Urinary Microscopy. *In* SCHRIER RW (Ed): *Manual of Nephrology*, Little, Brown and Company 1995: 120-36.
6. TIMIRAS PS: Aging as a stage of life, Common terms related to aging, Methods used to study aging. *In* TIMIRAS PS (Ed.): *Physiological Basis of Aging and Geriatrics*, CRC Press 2003: 3-10.
7. BOOTH AD, ALMOND MK, BURNS A *et al*.: Outcome of ANCA-associated renal vasculitis: A 5-year retrospective study. *Am J Kidney Dis* 2003; 41: 776-84.
8. WALTON EW: Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). *BMJ* 1958; 2: 265-70.
9. WATTS RA, GONZALEZ-GAY MA, LANE S, GARCIA-PORRUA C, BENTHAM G, SCOTT DG: Geoepidemiology of systemic vasculitis: comparison of the incidence in two regions of Europe. *Ann Rheum Dis* 2001; 170: 170-2.
10. GONZALEZ-GAY MA, GARCIA-PORRUA C, GUERRERO J, RODRIGUEZ-LEDO P, LLORCA J: The epidemiology of the systemic vasculitides in northwest Spain: Implications of the Chapel Hill Consensus Conference Definitions. *Arthritis Rheum* 2003; 49: 388-93.
11. FUJIMOTO S, UEZONO S, HISANAGA S *et al*.: Incidence of ANCA-associated primary renal vasculitis in Miyazaki Prefecture: The first population-based, retrospective epidemiological survey in Japan. *Clin J Am Soc Nephrol* 2006; 1: 1016-22.
12. WATTS RA, CARRUTHERS DM, SCOTT DGI: Epidemiology of Systemic Vasculitis: Changing Incidence or Definition? *Semin Arthritis Rheum* 1995; 25: 28-34.
13. GARCIA-PORRUA C, GONZALEZ-GAY MA: Comparative clinical and epidemiological study of hypersensitivity vasculitis versus Henoch-Schönlein purpura in adults. *Semin Arthritis Rheum* 1999; 28: 404-12.
14. GONZALEZ-GAY MA, GARCIA-PORRUA C: Systemic vasculitis in adults in northwestern Spain, 1988-1997. Clinical and epidemiologic aspects. *Medicine* (Baltimore). 1999; 78: 292-308.
15. DE LIND VAN WIJNGAARDEN RA, HAUER HA, WOLTERBEEK R *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: 2264-74.
16. HOGANSON DD, FROM AM, MICHET JR CJ: ANCA vasculitis in the elderly. *J Clin Rheumatol* 2008; 14: 78-81.
17. KAPLAN-PAVLOVCIC S, CERK K, KVEDER R, LINDIC J, VIZJAK A: Clinical prognostic factors of renal outcome in anti-neutrophil cytoplasmic autoantibody (ANCA)-associated glomerulonephritis in elderly patients. *Nephrol Dial Transplant* 2003; 18: v5-7.
18. UEZONO S, SATO Y, HARA S *et al*.: Outcome of ANCA-associated primary renal vasculitis in Miyazaki Prefecture. *Intern Med* 2007; 46: 815-22.
19. MUKTHYAR C. LUQMANI R: Disease-specific quality indicators, guidelines, and outcome measures in vasculitis. C*lin Exp Rheumatol* 2007; 25 (Suppl. 47): 120-9.
20. SLOT MC, TERVAERT JWC, FRANSSEN CFM, STEGEMAN CA: Renal survival and prognostic factors in patients with PR3-ANCA associated vasculitis with renal involvement. *Kidney Int* 2003; 63: 670-77.
21. BLIGNY D, MAHR A, TOUMELIN P, MOUTHON L, GUILLEVIN L: Predicting mortality in systemic Wegener's granulomatosis: A survival analysis based on 93 patients. *Arthritis Rheum* 2004; 51: 83-91.
22. WEIDNER S, GEUSS S, HAFEZI-RACHTI S, WONKA A, RUPPRECHT HD: ANCA-associated vasculitis with renal involvement: an outcome analysis. *Nephrol Dial Transplant* 2004; 19: 1403-11.
23. LANE SE, WATTS RA, SHEPSTONE L, SCOTT DGI: Primary systemic vasculitis: clinical features and mortality. *Q J Med* 2004; 98: 97-111.
24. REINHOLD-KELLER E, BEUGE N, LATZA U *et al*.: An interdisciplinary approach to the care of patients with Wegener's granulomatosis: long-term outcome in 155 patients. *Arthritis Rheum* 2000; 43: 1021-32.
25. GARCIA-PORRUA C, CALVINO MC, LIORCA J, COUSELO JM, GONZALEZ-GAY MA: Henoch-Schönlein purpura in children and adults: Clinical differences in a defined population. *Semin Arthritis Rheum* 2002; 32: 149-56.