Studies on the Epidemiology and Outcome of Primary Systemic Vasculitis

Mohammad, Aladdin

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Studies on the Epidemiology and Outcome of Primary Systemic Vasculitis

Av

Aladdin Mohammad
Leg. läkare

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Fakultetsopponenten
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Handledare
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Lunds universitet

Bitr. handledare
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Lunds universitet

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Abstract

Primary Systemic Vasculitides [PSV: Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), Churg-Strauss syndrome (CSS) and polyarteritis nodosa (PAN)] are rare systemic diseases of unknown etiology; if untreated, they are associated with high morbidity and mortality rates. Changes in the classification and diagnostic improvements during the last decades have increased reported prevalence and incidence rates of PSV. However, many uncertainties remain regarding the epidemiology of PSV. This thesis contains a comprehensive description of the epidemiology and outcome of PSV from a stable population in southern Sweden. (I) Using multiple retrieval sources, all prevalent cases with PSV within a defined population were identified to determine the point prevalence (p.p.) per January 1, 2003. Eighty-six patients fulfilled the study criteria for PSV, which equals a prevalence of 299 cases per million inhabitants (160 for WG, 94 for MPA, 14 for CSS and 31 for PAN). This is the highest prevalence figure ever reported for PSV. By capture-recapture analysis the case completeness was estimated to be 97%.
(II) The extent of irreversible organ damage, on the date of p.p., was measured using the Vasculitis Damage Index (VDI), for all the 86 patients from Paper I. Organ damage was very common in our patients, the medium VDI score was 3 and only 9% had not been assigned any item of damage. The most common type of damage was cardiovascular, followed by renal, neuropsychiatric and ear-nose-throat (ENT). ENT damage was more prevalent in younger while renal damage was more common in older patients.
(III) The annual incidence rate for the PSV was estimated during a10-year period in two healthcare districts in southern Sweden with a total population of 640 000. A total of 140 patients fulfilled the study criteria. The incidence rate for the whole PSV group was 21/million (9.8 for WG, 10.1 for MPA and 0.9 for CSS and PAN each). For all patients, absolute survival rates were 87.8% at 1 year, 71.6 % at 5 years and 55 % at 10 years. Survival was better for WG then MPA. High age and renal disease at onset were the strongest predictors for mortality. (IV) The possible influence of cigarette smoking on the development of permanent organ damage was studied using cases from Paper I. Data were analyzed from 77 patients for whom data on smoking habits were available. Patients smoking at onset tended to develop more renal and cardiovascular damage. However, none of those who smoked at the time of diagnosis subsequently developed ENT damage.

Key words: Vasculitis, ANCA, Wegener's granulomatosis, Vasculitis damage index, arteritis, survival, microscopic polyangiitis, polyarteritis nodosa, Churg-Strauss syndrome

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Aladdin Mohammad

LUND UNIVERSITY
Faculty of Medicine

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This thesis is based on the following Papers, which will be referred to by their Roman numerals.

I **Mohammad AJ**, Jacobsson L, Sturfelt G and Segelmark M: Prevalence of Wegener's granulomatosis, microscopic polyangiitis, Polyarteritis nodosa and Churg-Strauss syndrome within a defined population in southern Sweden. Rheumatology (Oxford). 2007 Aug; 46(8):1329-37.

II **Mohammad AJ**, Bakoush O, Sturfelt G, and Segelmark M: The pattern and extent of organ damage in small vessel vasculitis measured by the Vasculitis Damage Index (VDI). Scand J Rheumatol. 2009; 38:268-275.

III **Mohammad AJ**, Jacobsson L, Westman K, Sturfelt G and Segelmark M: Incidence and Survival rates in Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome and Polyarteritis nodosa. Rheumatology (Oxford). 2009, *in press*.

IV **Mohammad AJ** and Segelmark M: Association of cigarette smoking with organ damage in primary systemic vasculitis. Manuscript *submitted.*

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Contents

Abbreviations

AASV	ANCA associated systemic vasculitis
ACR	American College of Rheumatology
ANCA	anti-neutrophil cytoplasmic antibodies
Anti-CCP	anti-cyclic citrullinated peptide
AZA	azathioprine
BVAS	Birmingham vasculitis activity score
CHCC	Chapel Hill Consensus Conference
CNS	central nervous system
CSS	Churg-Strauss syndrome
CYC	cyclophosphamide
ELISA	Enzyme linked immunosorbant assay
EMEA	European Medicine Agency
ENT	Ear-nose-throat
ESRD	end stage renal disease
EUVAS	European vasculitis study group
FFS	five factor score
GFR	Glomerular filtration rate
GI	gastrointestinal
GN	glomerulonephritis
HLA	human leukocyte antigen
HSP	Henoch-Schönlein purpura
IIF	indirect immunofluorescence
IQR	inter-quartile ratio
MPA	microscopic polyangiitis
MPO	myeloperoxidase
MTX	methotrexate
NRN	national registration number
PAN	polyarteritis nodosa
PE	plasma exchange
PR3	proteinase3
PSV	primary systemic vasculitis
RA	rheumatoid arthritis
SLE	systemic lupus erythematosus
SMR	standardized mortality ratio
VDI	vasculitis damage index
WG	Wegener’s granulomatosis

1 Introduction

Vasculitis means inflammation of the blood vessel wall resulting in bleeding and disruptions of the blood supply, with subsequent dysfunction and damage to different organs in the body. The vasculitic process can affect blood vessels of any type, size or location in any organ. The signs and symptoms of vasculitis are non-specific, making the list of differential diagnoses long. A high level of suspicion is the key to diagnosis in vasculitic syndromes. Vasculitis may arise during the course of an underlying rheumatic, infectious or malignant disease, and is then referred to as secondary vasculitis. If there is no associated disease process, the vasculitis is said to be primary. Primary vasculitides constitute a heterogeneous group of diseases of unknown aetiology affecting blood vessels of different sizes and types. Immunosuppressive or cytotoxic agents are usually needed to bring the diseases into remission and to prevent progression to irreversible organ failure or death. The clinical consequences usually depend on the extent of the disease and the organs involved. Primary vasculitis can be benign or life-threatening and may affect only one organ like the skin (limited) or several organs such as the lungs, kidneys and central nervous system (systemic).

This thesis focuses on a group of diseases within the spectrum of primary systemic vasculitis, with many overlapping features, characterized by involvement of small and medium-sized vessels. If left untreated they result in potentially life-threatening manifestations, irreversible organ damage and high mortality. Historically, these diseases were known as the "PAN group" and have been studied collectively by many authors. Their prototype is polyarteritis nodosa (PAN). Three diseases in this group of primary vasculitis [Wegener's granulomatosis (WG), microscopic polyangiitis (MPA) and Churg-Strauss syndrome (CSS)] are associated with anti-neutrophil cytoplasmic antibodies (ANCA) and are collectively referred to as ANCA-associated systemic vasculitis (AASV). Hereafter in this thesis the acronym PSV (primary pauci-immune systemic medium and small vessel vasculitis) will be used collectively as a term for WG, MPA, CSS and PAN.

1.1 Classification of vasculitis

1.1.1 Historical background

In the medical literature, the first description of the systemic vasculitis, named periarteritis nodosa was presented by Kussmaul and Meier 1866[1] when they described a young patient with systemic manifestations like fever, malaise, weight loss, muscle aches and tenderness. The description was based on clinical and macroscopic features since the term "periarteritis" referred to the gross pathology findings of nodules along the course of the vessel [2]. For many years after Kussmaul and Maier's work, periarteritis nodosa and the alternative term polyarteritis nodosa (PAN) were names used for all vasculitides. Different syndromes of vasculitis are described in relation to their similarity or diversity from PAN. Klinger in 1932 described a "rhinogenic granulomatosis" that later became known as Wegener's granulomatosis [3,4]. In 1948, Davson et al. presented a number of cases with "periarteritis nodosa" who had the histopathology diagnosis of "widespread necrotizing glomerulitis" [5]. This, as regarded by many authors, was the first attempt that separated the condition known today as MPA from the classical PAN [6-8]. In 1951

Churg (clinician) and Strauss (pathologist) described a syndrome which now bears their name [9].
The interest in inflammatory vessel diseases grew and many case reports were published. The first successful attempt to create a classification for vasculitis was made by Zeek in 1952 [10]. In her review, she proposed the name necrotizing angiitis and presented five main groups of vasculitis (Table 1). Zeek's classification was used as an outline by a number of other proposals of classifications [11].

Table 1. Zeek's classification 1952

1. Periarteritis nodosa
2. Hypersensitivity angiitis
3. Rheumatic arteritis
4. Allergic granulomatous angiitis
5. Temporal arteritis

Adapted from Zeek [12]

In 1990, the American College of Rheumatology (ACR) developed a set of classification criteria for several types of vasculitis [13]. However, there were no criteria for MPA, and the ACR criteria did not include ANCA as a surrogate marker for vasculitis. To address these problems a consensus meeting was held in 1992 at Chapel Hill, North Carolina, USA, and presented definitions of nomenclature of vasculitis based on the histopathology characteristics and the size of the blood vessels involved [14]. Epidemiological studies have used both the ACR criteria and the Chapel Hill Consensus Conference (CHCC) definitions in parallel despite the overlap between MPA and PAN when applying these two sets of criteria, resulting in confusion in interpretation and comparison of the results of these studies. The most recent effort in the field of classification of vasculitis was the development of a consensus method for application of these criteria and definitions. An algorithm integrating the ACR criteria and the CHCC definitions was developed with support from the European Medicine Agency (EMEA) [15] to be used in epidemiological studies of AASV and PAN.

1.1.2 ACR classification criteria 1990

The ACR published a number of classification criteria for seven vasculitis diseases: giant cell arteritis [16], Takayasu arteritis [17], polyarteritis nodosa [18],Wegener's granulomatosis [19], Churg-Strauss syndrome [20], Henoch-Schönlein purpura [21] and hypersensitivity vasculitis [22]. Retrospective studies of 1020 cases of vasculitis submitted by 37 rheumatologists from the United States, Canada and Mexico formed the base for the development of these criteria. The vasculitis diagnosis made by the contributing physician was used as a "gold standard". The ACR criteria were designed to help distinguish individual types of vasculitis from others and intended to describe groups of patients in epidemiological studies. The criteria were not meant to be used as diagnostic criteria when applied to individual patients in clinical care [23]. The limitations of ACR criteria when used for diagnosis were studied in a prospective cohort of patients evaluated for vasculitis, where only 75% of the patients with vasculitis and as many as 21% of those with non-vasculitic diseases fulfilled the ACR criteria [24]. This limitation is evident especially when many physicians inappropriately use the ACR 1990 criteria in

daily clinical practice for diagnosis of vasculitis in individual patients. The ACR criteria for classification of WG, CSS and PAN are shown in Tables 2, 3 and 4 respectively.

Table 2. ACR 1990 criteria for the classification of Wegener's granulomatosis (WG)

Criterion	Definition
1. Nasal or oral inflammation	*Development of painful or painless oral ulcers or purulent/ bloody nasal discharge*
2. Abnormal chest radiograph	*Chest radiograph showing nodules, fixed infiltrate or cavities*
3. Urinary sediment	*Microhematurea or red cell casts in urine sediment*
4. Granulomatous inflammation on biopsy	*Histologic changes showing granulomatous inflammation within the wall of an artery or in the peri- or extravascular area (artery or arteriole)*

Adapted from Leavitt RY et al. [19]. The patient is classified to have WG if at least 2/4 criteria are present.

Table 3. ACR 1990 criteria for the classification of Churg-Strauss syndrome (CSS)

Criterion	Definition
1. Asthma	*History of wheezing or diffuse high-pitched rales on expiration*
2. Eosinophilia	*Eosinophilia >10% on white blood cell differential count*
3. Mononeuropathy or polyneuropathy	*Development of mononeuropathy, multiple mononeuropathies or polyneuropathy attributed to a systemic vasculitis.*
4. Pulmonary infiltrates, non-fixed	*Migratory or transitory pulmonary infiltrates on radiographs attributed to a systemic vasculitis.*
5. Paranasal sinus abnormality	*History of acute or chronic paranasal sinus pain or tenderness or radiographic opacification of the paranasal sinuses*
6. Extravascular eosinophils	*Biopsy including artery, arteriole or venule showing accumulations of eosinophils in extravascular areas*

Adapted from Masi AT et al. [20]. The patient is classified to have CSS if at least 4/6 criteria are present.

Table 4. ACR 1990 criteria for the classification of polyarteritis nodosa (PAN)

Criterion	Definition
1. Weight loss ≥ 4 kg	*Loss of 4 kg or more of body weight since illness began, not due to dieting or other factors*
2. Livedo reticularis	*Mottled reticular pattern over the skin of portions of the extremities or torso*
3. Testicular pain or tenderness	*Pain or tenderness of the testicle, not due to infection, trauma, or other causes*
4. Myalgias, weakness or leg tenderness	*Diffuse myalgias (excluding shoulder/hip girdle) or weakness of muscles or tenderness of leg muscles*
5. Mononeuropathy or polyneuropathy	*Development of mononeuropathy, multiple mononeuropathies or polyneuropathy*
6. Diastolic BP >90 mm Hg	*Development of hypertension with the diastolic BP higher than 90 mmHg*
7. Elevated BUN or creatinine	*Elevation of BUN >40 mg/dl, or creatinine>1.5 mg/dl, not due to dehydration or obstruction*
8. Hepatitis B virus	*Presence of hepatitis B surface antigen or antibody in serum*
9. Arteriographic abnormality	*Angiogram showing aneurysms or occlusions in visceral arteries, not due to arteriosclerosis, fibromuscular dysplasia or other non-inflammatory causes*
10. Biopsy of small or medium-sized artery containing PMN	*Histologic changes showing the presence of granulocytes or granulocytes and mononuclear leukocytes in the artery wall*

Adapted from Lightfoot RW et al. [18]. The patient is classified to have PAN if 3/10 criteria are present
BP: blood pressure; BUN: blood urea nitrogen; PMN: polymorphonuclear neutrophils.

1.1.3 The CHCC definitions 1994

A proposal for definitions of primary systemic vasculitis was presented by a group of scientists and physicians from different medical disciplines with extensive experience in systemic vasculitis. The aim of the meeting was to "reach consensus on the names for some of the most common forms of non-infectious systemic vasculitis and to construct root definitions for the vasculitides so named" [14]. The meeting emphasized that their aim was not to develop classification or diagnostic criteria for systemic vasculitis. In the CHCC proposal, the primary systemic vasculitis was defined according to the size of the blood vessels involved into large, medium-sized and small vessel vasculitis (Table 5). The proposal was based on the histopathology definition of various vasculitic diseases. However, the demonstration of a direct pathologic process such as granuloma was not considered as necessary. Non-invasive evaluation may identify an abnormality that predicts the presence of granuloma; similarly haematurea and proteinuria together with the presence of red cell cast suggests the presence glomerulonephritis (GN). One of the most important proposals was the separation between microscopic and classical form of polyarteritis nodosa (Table 6). According to the CHCC definitions, classical PAN (cPAN) is a disease of medium-sized and small arteries with no involvement of smaller vessels as arterioles, capillaries and venules. In addition, neither glomerulonephritis nor the presence of positive ANCA is a feature of cPAN. By this definition, the cPAN became a rare disease. The name "microscopic polyangiitis" was proposed as a preferred name to "microscopic polyarteritis", since the former is more appropriate for patients

who might have inflammation of venules and capillaries but do not have vasculitis in arteries [14]. Immunohistology has shown that MPA, along with WG and CSS, is a pauci-immune vasculitis with no or little vessel wall staining with immunoglobulins. This characteristic allows the differentiation from other immune complex vasculitis such as Henoch-Schönlein purpura (HSP) and cryoglobulinaemic vasculitis [7,14].

Table 5. Names and definitions of the systemic vasculitides according to the CHCC

Large vessel vasculitis
Giant cell (temporal) arteritis
Takayasu arteritis
Medium-sized vessel vasculitis
Polyarteritis nodosa (classic polyarteritis nodosa)
Kawasaki disease
Small vessel vasculitis
Wegener's granulomatosis
Churg-Strauss syndrome
Microscopic polyangiitis (microscopic polyarteritis)
Henoch-Schönlein purpura
Essential cryoglobulinaemic vasculitis
Cutaneous leukocytoclastic angiitis

Adapted from Jennette et al[14]

Table 6. Definitions of the PSV studied in this thesis according to CHCC

Name of the disease	Definition
Polyarteritis nodosa (classic PAN)	*Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries or venules.*
Wegener's granulomatosis	*Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium sized vessels (e.g. capillaries, venules, arterioles, and arteries). Necrotizing glomerulonephritis is common*
Churg-Strauss syndrome	*Eosinophil-rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels, and associated with asthma and eosinophilia*
Microscopic polyangiitis (microscopic polyarteritis)	*Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (i.e. capillaries, venules or arterioles). Necrotizing arteritis involving small and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs.*

Adapted from Jennette et al. [14]

1.1.4 The EMEA algorithm

A group of physicians interested in the epidemiology of systemic vasculitis met at the EMEA in London in September 2004 and January 2006. The aim of these meetings was not to create new classification criteria but to reach a consensus on the application of the available classification criteria and definitions to be used in epidemiological studies on PSV [15]. The result of these meetings was the adaptation of a classification algorithm applying the ACR criteria for CSS and WG 1990 [19,20] and the CHCC definitions [14] in a stepwise manner. The patient should have a clinical diagnosis of PSV before they

"enter" the algorithm to avoid including patients with other diagnoses. The algorithm incorporates surrogate markers for vasculitis and ANCA. The algorithm is applied in a hierarchic set as described elsewhere in this thesis (section 3.3). In its initial validation, the EMEA algorithm successfully categorized patients to a single diagnosis and there was good agreement between the classification by the algorithm and clinical diagnosis [15]. The algorithm has also been recently applied to a large cohort of 550 Chinese patients with PSV. The authors find the algorithm to be reproducible and only a few patients were left unclassified with no overlapping diagnoses [25].

1.2 Antineutrophil cytoplasmic antibodies

Antineutrophil cytoplasmic antibodies (ANCA) are auto antibodies against cytoplasmic constitutes of polymorphonuclear granulocytes. The first description of the method studying leukocyte autoantibodies detected by the fluorescent antiglobulin technique was presented by Calabresi et al. in 1959 [26]. In 1982; Davies et al. published a short report on 4 patients with segmental necrotizing glomerulonephritis having in their sera a factor that stained the cytoplasm of neutrophil leukocytes by indirect immunofluorescence, IIF [27]. In 1984, ANCA was described in 4 patients with systemic vasculitis; all had pulmonary involvement, and two had renal disease [28]. The association of ANCA with WG and the change in ANCA titre with disease activity was shown just one year later [29]. At least two patterns of ANCA: the cytoplasmic, cANCA, and the perinuclear, pANCA, can be visualized by IIF by adding patients' sera to ethanol-fixed neutrophil from healthy individuals [30]. However, difficulties in interpreting the IIF pattern[31], as well as the discovery that the c- and pANCA directed against different antigenic specificities[32,33], prompted the development of antigen specific assay using purified molecules as solid-phase ligand, the enzyme linked immunosorbant assay (ELISA). The cANCA detected by ELISA directed against proteinase-3 (PR3) [34]; while the pANCA is less specific and represent antibodies against myeloperoxidase (MPO)[33], elastase [32], lactoferrin[35] and bactericidal/permeability increasing protein, BPI-ANCA[36]. The association between ANCA specificities and clinical diagnosis of different vasculitis diseases is not certain. Even though, classical systemic WG is usually associated with PR3 ANCA and c-pattern on IIF[29,37,38], and the MPO ANCA and the p-pattern by IIF is seen most frequently in patients with MPA [39] and CSS[40]. However, ANCA detected by IIF is not specific for vasculitis and could be present in other inflammatory diseases such as inflammatory bowel diseases [41], rheumatoid arthritis (RA) [42], systemic lupus erythematosus (SLE) [43] and other forms of pulmonary diseases [44].

1.3 Clinical descriptions of PSV

According to the above criteria and definitions, the 4 diseases within the PSV group discussed in this thesis are described clinically as follows:

Wegener's granulomatosis (WG) is a chronic inflammatory granulomatous disease of unknown aetiology, most commonly involving the upper and lower respiratory tracts and kidneys, affecting small vessels and characterized by a course of relapsing and remitting inflammation [45-47]. Limited and systemic or severe WG are referred to as a mild disease limited to the upper or lower airways and a widespread life-threatening disease with multiple organ involvement or renal disease, respectively [48-51]. The most common clinical presentation in WG is the involvement of upper airways and the ear-

nose-throat (ENT) region with nasal congestion and sinusitis, epistaxis, hearing loss and subglottic stenosis [52-54]. Pulmonary involvement occurs in 31-63% [52-56]. Kidney disease is a common and serious manifestation in WG, reported in 11-77 % of patients at diagnosis [47,56-58] to 85% at any time during the course of the disease [47]. Peripheral neuropathy is frequent in generalized WG and reported in up to 84% [59], while central nervous system (CNS) involvement is rare [52]. Positive c/PR3-ANCA has been reported in 76-86% of patients with WG [58,60,61].

Microscopic polyangiitis (MPA) is a systemic necrotizing vasculitis involving small vessels like small arteries, arterioles, capillaries and venules; and usually associated with focal segmental glomerulonephritis with crescent formation without granuloma [6-8]. The disease may sometimes be preceded by prodromal symptoms characterized by "flu like" illness and arthralgia before fulminated systemic manifestation occurs [8]. Haemorrhagic pulmonary capillaritis occurring in 12-38 % [8,57,62], and renal involvement reported in 79-100 %, are the most serious features of MPA [8,56,57,62-64]. Relapse in MPA is common and reported in 34-60 % [64-66]. ANCA is frequently detected in patients with MPA; the majority is of p/MPO-ANCA where 56-81% had positive MPO compared to 10-39% with PR3-ANCA [62,64].

Polyarteritis nodosa (PAN) is a multisystem disease affecting medium- and small-sized arteries characterized by constitutional symptoms such as fever, weight loss, arthralgia [6,67-69]. Other symptoms include cutaneous, 30-50 % of cases [6,67-69], peripheral neuropathy such as mononeuritis multiplex in 50-70% [67-69], renal involvement in 60-80% [6,69], and abdominal pain, bloody diarrhoea reported in 34% of cases[6]. Angiography findings of multiple stenosis and dilatation, as well as microaneurysms, are highly suggestive of diagnosis [14,70]. HBV-related PAN has been reported in 36% of all patients with systemic disease [6].

Churg-Strauss syndrome (CSS) is a systemic granulomatous vasculitic disease that usually occurs in patients with asthma and or allergic rhinitis. In addition to asthma, patients usually have fever, hypereosinophilia and symptoms of cardiac failure, renal damage, and peripheral neuropathy resulting from widespread systemic vasculitis [9]. The most common clinical features reported in a selected series of patients were as follows: asthma 100%, generalized fatigue and weight loss 70-90%, sinusitis 61%, pulmonary infiltrates 53-76%, peripheral neuropathy 67-92%, central nervous system manifestations in 8%, gastrointestinal 33-47%, cardiac involvement 28-48%, renal involvement 12-67%[67,71-75]. MPO-ANCA was positive in 25-40 % of patients with CSS [71,76,77]

1.4 The evolution of treatment of PSV

There are no specific treatments for the different types of vasculitis. The main goals of treatment in PSV are (i) induction of remission, (ii) maintenance of remission, (iii) prevention of relapse and subsequent organ damage and (iv) prevention and treatment of drug toxicities. Untreated WG runs a rapid fatal course with a mean survival of 5 months and one year mortality rate of 80% [45]. The introduction of the use of corticosteroids in the 1940s for the treatment of PAN improved the survival rate [78]. In 1973, Fauci and Wolff published the first report on the successful use of oral cyclophosphamide (CYC) in 18 patients with generalized WG and demonstrated a striking response in 80% of the patients; these patients were still in remission 63 months following the initiation of

therapy [46]. Unfortunately, prolonged use of CYC and high dose prednisolone led to a variety of toxic side-effects such as sterility, major infections, haemorrhagic cystitis and development of cancer [79]. The use of intravenous pulse CYC (pCYC) regimen has been successfully introduced for patients with WG; it is effective in achieving remission with fewer side-effects compared with oral CYC but has been associated with a high relapse rate [80-84]. In a randomized control trial of oral CYC vs. pCYC run by the European vasculitis study group (EUVAS), there were no differences in the proportion of patients achieving remission at nine months [85]. The high rate of drug toxicity prompted investigators to use other less toxic drugs, such as methotrexate (MTX), for remission induction especially in patients with no life-threatening disease [49,86]. Patients suffering from life-threatening manifestations such as pulmonary haemorrhage or rapidly progressing renal failure usually need more aggressive therapy than CYC and steroids. A European multicenter trial found that plasma exchange (PE) led to better renal survival as compared to i.v. methylprednsiolone [87].

Patients achieving successful remission induction are today usually maintained on less toxic agents. In the CYCAZAREM trial, the withdrawal of CYC and the substitution of azathioprine (AZA) after remission did not increase the rate of relapse, and there was lower toxicity in the AZA group because of the shorter duration of exposure to CYC [88]. Other agents used to maintain remission include MTX [89,90], mycophenolate mofetil [91,92], i.v. immunoglobulin [93,94], and leflunomide [95,96]. Treatment with trimethoprim/sulphamethoxazole reduces the incidence of relapses in patients with WG compared with placebo [97], induces remission in more than half of the patients with "initial phase" WG [98] and is used as prophylaxis against *pneumocystis jiroveci* (formerly *p. carinii*) in patients treated with CYC[84].

Patients with hepatitis B virus-related PAN should be considered as a special group to treat. The regimen described by the French Vasculitis Study Group favoured the use of antiviral therapy and PE over the conventional therapy with CYC and corticosteroids [6,99].

The use of anti-tumour necrosis factor alpha (anti-TNF-α) in vasculitis has proved to be controversial. In a randomized placebo control trial to evaluate etanercept for treatment of 180 patients with WG, durable remissions were achieved in only a minority of the patients, and there was a high rate of treatment-related complications as well as an increased rate of solid malignancies [100,101]. However, some other smaller studies revealed more encouraging results with infliximab [102-104]. Rituximab, anti-CD 20 monoclonal antibodies approved for the treatment of malignant lymphoma has been used in AASV and was effective in treating refractory cases of WG [105-110].

1.5 Epidemiology of PSV

1.5.1 The descriptive epidemiology

During the last twenty years a number of studies have been published addressing the epidemiology of PSV in Europe, Japan, USA, New Zealand and Australia. Many of the studies used the ACR criteria 1990[13] and the CHCC definitions (CHCC) [14]. As discussed above, neither of these criteria is sufficient enough to identify or define all patients with PSV. In spite of such criticism, the introduction of ACR 1990 criteria

and the 1994 proposal on nomenclature by the CHCC has significantly improved the possibilities of doing epidemiological research.

1.5.2 Incidence of the PSV

Old epidemiologic studies reported incidence rates on the "PAN group". Population-based estimates of the incidence rates range from 4.6/million in UK [111] and 77/million in a hepatitis B endemic area in Alaska[112]. The combined annual incidence of WG and MPA was reported to be 1.5/million in the beginnings of 1980s in UK [113]. Thus, reported incidence rates of the diseases within the PSV group were varied depending on the time period of the study and disease definitions that have been used.

During the last two decades, studies showed a clear increase in the incidence rates of some or all of the diseases within our current understanding of the PSV, Table 7. The overall incidence rates of PSV are reported to be 13.07-18.3/million in Spain[114,115], 19.8/million in UK[116], and 13.7 in Australia[117]. The differences between incidences might be explained by regional/geographical variations but also could be even due to classification criteria or definitions used. One study from Spain used the CHCC definitions which are more restrictive than the ACR criteria used by studies from the UK. The age-specific incidence for the whole group of PSV showed a clear increase with age. Two studies reported a peak incidence in the age group 55-64 years [114] and 65-74 years [116], respectively. The PSVs were slightly more common in men [114,116].

The most studied disease in the PSV group is WG; while data on MPA are scant since it was not until the publication of the CHCC 1994 when MPA had received its first definition. For PAN it is even more difficult to extract epidemiological figures applicable to our current understanding of the disease because different definitions have been used over the years [118]. Most of the epidemiological studies showed a significant increase in the incidence of WG during the last 20 years [54,119-121]. This increment, believed to be due to several factors such as increased awareness, the introduction of ANCA as well as genuinely increased incidence rates, could be an important factor. A comparison study from two regions in Europe showed overall incidence rates of all PSV to be quite similar; about 19/million [115]. There were, however, differences in the incidence of WG and MPA between northern and southern Europe; where WG is more common in the North while MPA is more common in the South of Europe [115]. In line with this theory, the incidence of WG in southern Germany is lower than in the UK and Norway and higher than the incidence rate in Spain [122]; the incidence of MPA in Norway is lower than in the UK and much lower than in Spain [123]. However, there was no "reciprocal" south-north gradient in the incidence of WG between northern and southern areas in the southern hemisphere; studies from New Zealand and Australia showed quite similar incidence rates of WG, comparable with the incidence rate in northern Norway [60,117]. The highest incidence of MPA ever recorded was from Kuwait 24/million [124]. According to the authors; this exceptionally high figure might be explained by the methodology and approach to the diagnosis procedure.

For PAN; studies using the ACR 1990 criteria reported incidence rates of between 1.1 and 8/million [116,117,125]; while studies strictly applying the CHCC definitions showed much lower incidence rates; ranging from no cases to 2.5/million [69,114,116,122]. However, there is a very high incidence rate of 16/million reported from Kuwait in a study utilizing histopathology and angiography findings in diagnosis establishment in

patients with renal vasculitis [124].
CSS has been studied previously within the PAN group. In France, the disease represented 20% of the systemic vasculitides group of PAN [6]. The highest incidence rate was reported from Norwich in the UK, 2.7/million [116], and recently from Australia 2.3/million [117]. The HBV-related PAN constitutes about one third of all systemic PAN cases in France [126]. Studies have also shown another pattern of geographical differences in the epidemiology of PSV. The first population-based epidemiologic study from Miyazaki in Japan had showed no cases of WG or CSS but a very different prevalence of ANCA serology with more than 90% was MPO-ANCA [127]. Another comparison study between Japan and the UK revealed a similar incidence rate of renal vasculitis; but no cases with PR3-ANCA associated vasculitis were seen in Japan, and WG was much less common there than in the UK [128].

1.5.3 Prevalence of the PSV

There are relatively few prevalence estimates compared with incidence studies of PSV, recent estimates spans between 46-184/ million [117,129], Table 8. Prevalence figures tend to increase over time since they are affected by increasing incidence as well as better survival. The improved case identification by the use of multiple retrieval sources in many studies could be another important factor explaining the increasing prevalence of PSV.
In a study utilizing multiple sources of case retrieval including ANCA databases, applying the CHCC definition, the prevalence of WG in North and South Germany was 58 and 42 per million, respectively, and it was the next in order of frequency after giant cell arteritis [129]. The prevalence of WG was lower in the USA, New York, and it was 30/million [130] when the use of hospitalizations and death certificates as retrieval sources might have an important effect on the low figure as mild cases or those not hospitalized were never identified. However, in a recently conducted study from the state of Western Montana, USA, the prevalence of WG was estimated to 90/million with the case identification using a survey including all regional rheumatologists, pulmonologists, nephrologists, otolaryngologists as well as mortality records [131]. A study from a “pure” urban multiethnic area from Paris has also shown a low prevalence of WG, 23.7/million [132]. The point prevalence of WG in Norway increased from 30.4/million in 1988 to 95.1/million in 1998 [54]. From the southern hemisphere, the prevalence of WG was estimated to 112/million in New Zealand and 95/million in Australia [60,117]. Studies on MPA showed variable figures, from no cases in southern Germany to 25.1/million adults in Paris, 30/million in USA, and 37 and 39/million in New Zealand and Australia, respectively [60,117,129,131,132]. The figure for PAN, the most prevalent disease in Paris among the PSV group, was 30.7/million [132]. The differences of prevalence figures of PAN were probably due to the diversity of definitions discussed above. In the Parisian study, the definitions used (including HBV-related PAN) were “more sensitive than the CHCC and more restrictive than the ACR” as described by the authors [132]. Prevalence figures of CSS were comparable in Europe, reported at between 10.7 in Paris [132] and 13 in Norway[133] while the lowest prevalence in Europe was reported from Germany[129]. However, the highest prevalence reported so far was from Australia, 22 cases/million [117].

Table 7. Selected studies on the incidence of PSV

Country (area)	Author [Reference]	Study period	Population	Criteria	Diseases	Incidence/ million
Australia (capital territory/ Se-New South Wales)	Ormerod [117]	1995-2004	430 000		PSV	13.6
				ACR	WG	8.6
				CHCC	MPA	3.6
				ACR	CSS	2.2
				ACR	PAN	1.7
Australia (south Australia)	Hissaria [134]	2001-2005		ACR	WG	11.2
Kuwait (Kuwait city)	El-Reshaid [124]	1993-1996	122 000	CHCC	MPA	24
					PAN	16
Spain (Northwest)	Gonzales-Gay [135]	1988-1997	250 000	ACR	WG	4.7
				CHCC	MPA	9.4
				ACR	CSS	1.06
				ACR	PAN	6.8
Spain (Northwest)	Gonzales-Gay [114]	1998-2001	239 000	CHCC	WG	2.95
					MPA	7.91
					CSS	1.31
					PAN	0.90
Germany (North/South)	Reinhold-Keller [122]	1998-1999	4 881 000	CHCC	WG	7/5.5
					MPA	2.7/1.5
					CSS	0.5/1
					PAN	1.5/1
Germany (North)	Reinhold-Keller [136]	1998-2002	2 777 000	CHCC	WG	8.6
					MPA	2.7
					CSS	1.1
					PAN	0.9
UK (Norfolk)	Carruthers [119]	1988-1993	515 000	ACR	WG	8.5
UK (Norfolk)	Watts [116]	1988-1997	413 000	ACR	WG	9.7
				CHCC	MPA	8.0
				ACR	CSS	2.7
				ACR	PAN	8.0
Sweden (nationwide)	Knight [120]	1975-1985	8 000 000	ACR	WG	3
		1986-1990				8
		1991-2001				12
Sweden (Örebro)	Tidman [137]	1975-1995	273 000	CHCC	PSV	21
Norway (Tromso)	Koldingsnes [54]	1984-1988	464 000	ACR	WG	5.2
		1989-1993				6.2
		1994-1998				12
Norway (Tromso)	Watts[123]	1988-1998	?		PSV	13.7
				ACR	WG	10.5
				CHCC	MPA	2.7
				ACR	CSS	0.5
				ACR	PAN	4.4
Finland	Takala [121]	1981-1985		ACR	WG	1.9
		1986-1990				3.6
		1991-1995				6.0
		1996-2000				9.3
Sweden (Lund)	Selga[69]	1990-2002	283 000	CHCC	PAN	1.6

Table 8. Selected studies on the prevalence of PSV

Country (area)	Author [Reference]	Study period	Population	Criteria	Diseases	Prevalence/ million
New Zealand (Centerburg)	Gibson [60]	2005	481 000	ACR CHCC	WG MPA	93.5 37
Australia (capital territory/ Se-New South Wales)	Ormerod [117]	2000-2004	430 000	 ACR CHCC ACR ACR	PSV WG MPA CSS PAN	184 95 39 22 22
France (Paris)	Mahr [132]	2000	1,094 000	 ACR CHCC ACR ACR	PSV WG MPA CSS PAN	90.3 23.7 25.1 10.7 30.7
Germany (north/south)	Reinhold-Keller [129]	1994	876 000	CHCC	WG MPA CSS PAN	58/42 9/0 7/2 9/2
UK	Watts [116]	1997	429 000	ACR/ CHCC	PSV WG	144.5 62.9
Norway	Haugeberg [133]	1996	150 000	ACR	WG CSS PAN	53 13 33
Norway (Tromso)	Koldingsnes [54]	1988 1993 1998	464 000	ACR	WG	30.4 49.3 95
USA (New York)	Cotch [130]	1990	?	ACR	WG	30

1.5.4 The analytical epidemiology

1.5.5 The aetiology of PSV

The aetiology and pathogenesis of PSV are incompletely understood. Epidemiological studies from different parts of the world help to increase our knowledge on the PSV included environmental and genetic factors that might play an important role in the aetiology of these diseases. Many reports from epidemiological studies indicate that multiple risk factors may be involved in susceptibility to vasculitis, including environmental factors, genetic predisposition, drugs and infections.

A significant association has been found between both WG and MPA and farming, indicating an important role for **environmental factors** [138]. In a case control study, the percentage of patients with AASV reporting exposure to silica dusts was significantly higher than their controls [139]. Occupational silica exposure was associated with a significantly higher risk of developing ANCA associated rapidly progressive GN [140] and WG with renal involvement than non-exposed individuals [141]. However, in another case control study, more than 75% of the participants, including the control group, reported a high rate of environmental exposure to inhaled particles, a finding that may reflect a more important role of host susceptibility [142]. In contrast, a newly published study from Sweden using the Swedish population censuses, information on employment and the register of inpatient care as a source of information; no occupational risk for WG has been found [143].

Unknown environmental factors may influence the differences in development of PSV

in rural areas compared to large cities. Differences in the occurrence of WG between different geographical areas had been found in a study from New York State [130]. Moreover, in a recent study from the capital territory of Australia, the incidence of MPA and WG was higher in rural than in urban areas [117]. However, such differences were not evident in studies from Germany and Spain [114,129]. Differences in life style, occupation and the degree of pollution between urban and rural areas might have some impact on the development of PSV.

Genetic factors have also been discussed as an important factor in the aetiology of PSV. Studies on WG found that the disease is more common in white Americans than African Americans [52,144]. In a study on a multiethnic population from Paris; the prevalence of PSV was 2.0 times higher for subjects of European descent than emigrants [132]. Other genetic suggestions come from a number of reports on familial aggregation of WG [145]. However, a recent population based study from Sweden showed low occurrence of WG among close biologic and non-biologic relatives of patients with WG [146]. Finally, the linkage between developments of PR3-ANCA associated vasculitis with the PIZ-phenotype of alpha1-antitrypsin deficiency [147] adds to the evidence of possible genetic predisposition. Patients exhibiting the PIZZ-phenotype have a much higher incidence of small and medium-sized vasculitis than background general population [148].

There is evidence of a temporal association between the use of some **drugs** and the development and deterioration of vasculitis. Treatment with granulocyte stimulating factors (G-SF) can cause vasculitis or vasculitis mimicker, and drugs like hydralazine or propylthiouracil were reported as triggering factors in ANCA-positive vasculitis [149]. The possible association between the use of leukotriene antagonists and the development of CSS in some patients with asthma has been speculated but such association is not very clear [150,151].

There is increasing evidence of the association of different bacterial and viral **infections** with vasculitis [152,153]. In WG, chronic nasal carriers of *Staphylococcus aureus* are more prone to relapse, suggesting a role of infection in the pathogenesis of WG and a possible clue for treatment [154,155]. Other indirect evidence of a possible association between vasculitis and infections is that reported by Raynauld et al. who have seen a seasonal variation in the onset of WG with a greater onset in the winter [156].

1.5.6 Seasonal variation

The seasons for the onset of vasculitis have been investigated in a number of epidemiological studies on PSV, Table 9. The importance of investigating the seasonality of PSV is to try to understand the possible aetiological or triggering factors of these diseases. As discussed above, linkage between the onset of WG and infections has been addressed previously by many investigators. More onsets in the summer may favour the allergy theory while greater onset in the winter months might support the infection theory. Differences in methodology, study design and objective might explain the different results among studies. Most studies were retrospective in nature, collected their data from available patient records or by telephone interviews [157]. The data collection by these methods may cast a doubt on the accuracy of results because of documentation and recall problems. WG is the most studied disease regarding the seasonal variations. The onset of WG has been found to be increased in summer in one study [157], and in winter in other studies[119,156], while no seasonal variation was found in yet other

studies [54,130,134,142,158,159]. An increased onset in winter was also found in one study of patients with positive cANCA, but no differences were found between the studied disease phenotypes [137].

Table 9. Selected studies on seasonal variations at onset of vasculitis

Country	Authors/ reference	Year of publication	Disease studied	Seasonal variation?	Comments
USA	Falk[160]	1990	AASV/ANCA associated GN	YES: winter	Results given for all studied diseases
USA	Raynauld [156]	1993	WG, PAN and GCA	YES: winter	Results were only applicable to WG, no seasonal variation for PAN and GCA
UK	Carruthers[119]	1996	WG	YES: winter	
Sweden	Tidman [137]	1998	AASV	YES: winter	High incidence in winter only in patients with pos. cANCA
Italy	Pavone[57]	2006	WG and CSS MPA	YES: autumn and winter YES: spring and summer	CSS slight tendency
France	Mahr[157]	2006	WG	YES: summer	Study designed to address the seasonal variation.
USA	Cotch[130]	1996	WG	NO	
Germany	Aries[158]	2008	WG	NO	Large study, 445 patients over a period of 36 years
Norway	Koldingsnes [54]	2000	WG	NO	
USA	Duna [142]	1998	WG	NO	
UK	Lane [159]	2007	WG	NO	
Australia	Hissaria [134]	2008	WG	NO	

1.6 Outcome measures in PSV

1.6.1 Survival studies

The survival rates found in different studies varied according to the criteria and definitions used for patients inclusion, as some studies included patients according to the diagnosis phenotypes while others stratified patients according to the presence of renal or pulmonary involvement. Most studies of survival among patients with PSV are based on either cohort studies from large tertiary referral centres or clinical multicentre studies [56,58,88,161-163]. Both these types are associated with a substantial risk of sampling bias. Clinical studies always contain exclusion criteria that frequently limit access to elderly persons and other patients with poor prognosis, and such patients are less likely to be sent to referral clinics. Only one study gives a combined survival rate for the whole PSV group according to the definition used in this thesis; the 1- and 5-year survival rates for PSV were 84.8% and 65.5 %, respectively [56]. Selected survival studies are shown in Table 10 for WG and Table 11 for MPA.

For WG, the 1- and 5-year survival rates were between 76-100% and 65.9-91.5%,

respectively. In the case of MPA, the corresponding figures ranged between 81-96% and 45-76%. In WG, the 10-year survival rate was between 75-88% [164], while in another study on patients with WG, all with renal involvement, the survival rate was 59% [55]. The survival rates for MPA is worse compared with WG, possibly because of a higher rate of renal involvement in MPA, though studies including only patients with renal disease found no such differences [64,165,166]. The survival rate was also worse for patients with MPA and alveolar haemorrhage with a 5-year survival of 68% [167]. The degree of creatininemia might have some impact on the figures of survival, as it seems that survival rates decrease with increased serum creatinine level. The 5-year survival figures for WG patients with renal involvement who had a mean creatinine of 556 μmol/l and a median of 251 μmol/l are reported to be 69.5% and 74 %, respectively [55,168]. However, in one study of 37 WG patients with renal involvement and a median serum creatinine of 173μmol/l, the 5 year survival was 91.5 % [169]. For CSS, the 1- and 5-year survival was reported to be between 83-94% and 60-97%, respectively [56,164]. In a large French study with a cohort of 96 CSS patients, the survival rate after 78 months of follow-up was 72.3% [74].

Age at diagnosis and serum creatinine level were the most common predictors of mortality in the majority of survival studies (Table 10 and 11). Excess of organ damage, hepatic involvement and high urine-IgM have also been reported as predictors of mortality. However, the presence of ENT involvement seems to have a protective effect against death in three studies of WG (Table 10). Another predictor of mortality in patients with PSV is the Five Factor Score (FFS), a prognostic core set of clinical and laboratory data (proteinuria 1 g/day, serum creatinine>140μmol/L, severe GI tract involvement, cardiomyopathy and the presence of CNS involvement) giving a score of one to each item, found to be significantly associated with poor outcome [170]. A new version of the FFS, presented recently, revealed that sinus involvement in WG was protective against mortality [171]. The presence of excess of organ damage, measured by the vasculitis damage index (VDI), has been used as a predictor of mortality. The baseline permanent organ damage assessed by the VDI was one of the most important factors; besides high age and dialysis-dependency that associated with reduced survival [61]. In patients with PR3-ANCA positive vasculitis, the survival rate for the PiZ gene of α1-antitrypsin carriers was significantly lower than for the non-carriers [172]

The standardized mortality ratio (SMR) expresses the overall mortality of patients compared with the general population. Previous studies reported SMR between 1.6 and 4.8 in patients with PSV, Table 12.

Table 10. Selection of studies on patient survival in Wegener's granulomatosis

Authors[reference]	Year	no. of patients	1-year survival	5-year survival	Predictors of mortality and comments
Mattesson[144]	1996	77	90%*	75 %	Granuloma on biopsy
Haubitz[173]	1998	35	100%	79%	All patients with ESRD and were on chronic dialysis
Aasarod[55]	2000	108	93%*	74 %	Age at inclusion and low serum albumin
Reinhold-Keller[174]	2000	155	99%	-	Age, nephritis
Mahr[58]	2001	49	76%*	-	Age, creatinine, no ENT involvement
Koldingsnes[61]	2002	56	93%	79 %	Increased age, dialysis dependence , organ damage
Bilgny[175]	2004	93	-	74 %	Age, no ENT involvement
Weidner[176]	2004	32	-	73%*	
Little[168]	2004	31	90%*	65.9%	
Lane[56]	2005	99	85.5%	75,9 %	
Pavone[57]	2006	36	89%*	73%*	Age, cerebral, renal, hepatic involvement, no ENT involvement#
Bakoush[169]	2006	37	97%	91.5%	High age, increased urine-IgM

Not significant, only tendency

* Figures estimated from the Kaplan-Meier curves

Table 11. Selection of studies on patients' survival in microscopic polyangiitis

Authors[reference]	Year	no. of patients	1-year survival	5-year survival	Predictors of mortality and comments
Guillevin[62]	1998	85	86%*	74 %	FFS
Lauque [167]	2000	29	82%	68%	All patients had alveolar haemorrhage
Weidner[176]	2004	48	-	73%*	Age, creatinine
Little[168]	2004	33	85%*	76 %	Karnofsky score, intensity of treatment
Lane[56]	2005	24	82.7%	45 %	Age>65 years
Pavone[57]	2006	16	81%*	65%*	Cerebral ,renal, hepatic involvement
Bakoush[169]	2006	46	87%	63 %	High age, increased urine-IgM

Figures estimated from the Kaplan-Meier curves

Table 12. Standardized mortality ratios (SMR) in patients with PSV

Authors [reference]	Year	Diseases	no. of patients	SMR	95% CI
Mattesson[144][3]	1996	WG	77	4.6	SD ±0.65
Aasarod[55]	2000	WG	108	3.8	2.6-5.6
Booth[165][3]	2003	AASV	246	3.6	1.56-7.12
Lane[56][3]	2005	PSV	99	4.8	2.9-6.6
Eriksson[163][3]	2008	WG and MPA			
[1]Cohort 1			32	1.6	0.6-3.2
[2]Cohort 2			63	2.5	0.93-5.52

Diagnosis [1]before and [2]after 1996. [3]Results shown for 5-year survival

1.6.2 Organ damage

Better survival in PSV with an increasing number of prevalent patients has created a need for more refined outcome measurements than crude survival rates. The vasculitis damage index (VDI) is today the only validated clinical instrument available to assess irreversible organ damage in patients with systemic vasculitis. The VDI score was developed by Exley et al. in 1997 and consists of a list of about 64 items of damage grouped in 10 organ systems and one general category labelled "other damage" [177], Table 15. Damage is expressed as the total VDI score, where each item adds one point, and can also be expressed as critical damage (items of damage consistent with significant organ failure) and as systems score (the number of systems in which patients assigned at least one item of damage). Severe organ damage is defined as total VDI score ≥5, critical damage ≥1 and/or system score ≥3 [178]. The VDI registers all kinds of damage developed since the onset of vasculitis irrespective of whether they are caused by vasculitis disease, its treatment or any associated morbidity.

The VDI has been used in the assessment of organ damage in a number of therapeutic trials[87,88,179,180], and in one population based study on WG[61].

Damage is a common clinical problem in patients with PSV; only a few or no patients at all are not assigned any items of VDI at the time of assessments in different studies [88,177,179]. Damage occurs early on in the course of disease and there was a significant increase in damage during the follow-up time [87,88,179,181]. In a population based cohort study from Norway including 56 patients with WG followed for a median of 56.5 months; the rate of increase of VDI was six times greater during the first 6 months than the next 18 months (mean VDI at baseline 0.8, at 6 months 3.6 and at 24 months 4.7) [61]. For WG, the median VDI score was 2 after a medium follow-up of 25 months in one study and 6 after 42 months in another study [61,179]. In patients with MPA, the median VDI score significantly increased from 0 at presentation to 3 at six months [181]. The most common organ damage reported in patients with WG during a follow-up period of 42.5 months was renal (proteinuria; 61%), ENT damage (nasal and sinus dysfunction; 61%), peripheral neuropathy (43%) and arterial hypertension (38%) [61]. Similarly, a study on organ damage in a large cohort of WG, reported the greatest damage in the ENT region (hearing loss; 26%) followed by renal damage (proteinuria; 19%) [179].

Data on VDI estimates PAN are very scanty. The VDI score was applied to a cohort of 10 patients with PAN (of whom three patients were included in Paper III) defined according to the CHCC and followed for a median time of 6 years between 1990 and 2002[69]. The median VDI scores at 1 and 5 years after diagnosis were 1(range 0-5) and 2(1-5), respectively, and were significantly correlated with the disease activity at presentation, assessed by the Birmingham Vasculitis Activity Score (BVAS)[182]. At 1 and 5 years after diagnosis, the most common kinds of damage were cardiovascular and neuropsychiatric followed by renal damage [69].

The type of organ damage also differs between younger and older patients with an excess of treatment-related damage in older patients with systemic vasculitis [178], while patients with WG who sustained ENT damage were younger than patients without ENT problems[61].

Though it is not ideal, the VDI score is the only validated instrument in use, and efforts have been made to improve it and present a weighting system to give a more precise picture of the significance of damage scored in patients with PSV. Recently, an

international cooperation, using the data collection form Combined Damage Assessment (CDA) which includes items of damage from VDI and ANCA-associated vasculitis index of damage (AVID), attempted to develop a weighting system of different items of damage by obtaining expert views on the clinical relevance of different items [183]. In this expert rating of damage, a scale from 0 to 10 was to be assigned to estimate the clinical severity of each item, where 10 represented the most severe form. It is, however, too early for this rating system to gain acceptance before more extensive validation has been carried out.

1.6.3 Cigarette smoking and inflammatory diseases

Epidemiological studies have demonstrated significant associations between cigarette smoking and a number of inflammatory diseases. Smoking increased the risk of developing a number of rheumatic diseases such as seropositive rheumatoid arthritis (RA)[184-187], Systemic Lupus Erythematosus (SLE)[188] and giant cell arteritis (GCA)[189,190]. The association of cigarette smoking with inflammatory bowel diseases is complex. While ulcerative colitis is a non-smokers' disease, patients with Crohn's disease experience deterioration in disease manifestation when they smoke [191]. It is also reported that cigarette smoking is negatively associated with focal sialadenitis in lower lip biopsy in patients with primary Sjögren's syndrome [192],while the cessation of smoking can activate the mucocutaneous symptoms, especially oral aphthous lesions, in patients with Behçet disease [193]. A recently published German study suggested that smoking might reduce the risk for developing AASV [194]. There are no previous studies addressing the possible effect of smoking on the development of organ damage in vasculitis.

2 The aims of this thesis

The aims of this work were:

1. To develop and validate a search method to retrieve patients with PSV in the Swedish medical system.
2. To determine the prevalence of PSV (WG, MPA, PAN and CSS) in a geographically defined population in southern Sweden,
3. To determine the incidence of PSV in a geographically defined population in southern Sweden.
4. To estimate the survival of PSV from a population perspective.
5. To estimate the extent and pattern of organ damage in PSV in a defined population from a point prevalence perspective.
6. To study the association between smoking habits and the development of organ damage in PSV

3 Methods

3.1 Study area and population

The study area is located in Skåne, the southernmost region of Sweden. There are some geographical differences between Skåne and the rest of Sweden. The agricultural land in Skåne covers about 49.4% of the whole area as compared to only 7.9% for the whole area of Sweden. Still, only 2.5% of all employees work in agriculture, forestry, hunting and fishing. The number of people in Skåne employed in the areas of agriculture, research and education is somewhat higher than the national average. About 57.2% of the employees are working within the sectors of trade, healthcare, mining, manufacturing and energy supply. The health service in Sweden is available to all, both primary healthcare and specialized health services provided by hospitals. Referrals to specialist care are common but not mandatory.

The study area in **Papers I, II and IV** was a healthcare district (Mellersta Skånes sjukvårdsdistrikt) situated in the southwest of Skåne. The total population of the study area on December 31st, 2002 was 287 479, representing 3.2 % of the total population in Sweden[195]. The study area is 2832 km² (about 0.6% of the total area of Sweden) and is divided into 10 municipalities. There are several suburban communities from where a large percentage of the working population commutes to the cities of Lund and Malmö. The area is served by two hospitals: Lund University Hospital (referral hospital for the 1 575 000 inhabitants in southern Sweden) and Landskrona Hospital.

For **Paper III** another healthcare district was added (sydvästra Skånes sjukvårdsdistrikt). The two healthcare districts contain together 14 municipalities with a total population at the beginning of the study period in 1997 of 616 287, which increased to 667 240 by December 31st, 2006[196]. The population density in the study area was 202/km^2 as compared to 22 for the whole country. Females made up 50.4% of the study population and the age distribution was as follows: 0-14 years 18.8%; 15-54 years 54.6 %; and >55 years 26.6%

3.2 Retrieval of patients and case ascertainment

Case retrieval, ascertainment and classification were carried out as a four-step process, Table 13. First, lists of names and national registration numbers (NRN) were generated by searches in databases. Doublets were removed by the fact that NRN is unique for each individual living in Sweden. The number is composed of 10 digits – six indicating date of birth plus four, of which one indicates gender. The NRNs are used as matching criteria in these studies.

In the next step the lists were compared with the population register in Sweden (folkbokföringen). Patients not living in the study area at the day of point prevalence (study I) or day of diagnosis (study III) were removed to generate new lists. In the next step all available case records were pulled out in order to confirm a diagnosis of vasculitis, and finally, patients fulfilling the criteria for PSV were classified as WG, MPA, PAN and CSS using to the EMEA algorithm (see Diagnosis and classification).

In **Paper I** patients were retrieved from a multitude of local registries and databases serving departments and laboratories both inside and outside the study area. The databases can be broadly divided into three main categories: clinical, pathology and

serology databases.

The **clinical databases** were searched using the International Classification of Diseases 9 and 10 (ICD-9 and ICD-10). Searches were performed in the records (in- as well as out-patients) at all departments at Lund University Hospital known to see patients with vasculitis, this included the following departments: rheumatology, nephrology, general internal medicine, pulmonology, cardiology, gastroenterology, ophthalmology, otorhinolaryngology, dermatology, infectious diseases and paediatrics. Searches were also done at the Department of Medicine at Landskrona Hospital, and at hospitals nearby the study area (Malmö University Hospital, Helsingborg Hospital, and Trelleborg Hospital). In a similar way, searches were carried out at the largest private clinic in the area as well as two arbitrarily chosen primary healthcare centres in the study area.

The second main retrieval source was the **serology databases** of the two laboratories performing ANCA analysis in the area: the clinical immunology laboratory at Lund University Hospital and the private Wieslab AB in Lund. We asked the laboratories to provide lists of patients exhibiting a positive test for ANCA at any time between January 1997 and December 2002.

The third retrieval source was two **pathology databases**. A free word search was carried out at the Department of Pathology at Lund University Hospital using the Swedish word for vasculitis (vaskulit) to identify all patients where the word vasculitis was mentioned in the pathology report. The second database was the renal biopsy register, a comprehensive prospective clinical and pathology register including all patients who have undergone renal biopsy at 8 reporting hospitals in Southern Sweden. The search was made for the diagnosis terms "Wegener's granulomatosis" and "microscopic polyangiitis" as well as the pathologic term of crescentic and necrotizing glomerulonephritis.

For **Paper III** we reused all relevant lists from Paper I, covering the period 1997-2002. We then, at yearly intervals, performed new searches using a simplified search algorithm based on our findings in Paper I. These searches were made at the Department of Rheumatology and Nephrology at the Lund and Malmö University Hospitals looking for patients assigned ICD-10 codes between M300 and M320 as well as at Wieslab AB, looking for patients positive for PR3- and MPO-ANCA.

Table 13. The steps of patient retrieval

Step 1	Step 2	Step 3	Step 4
Lists of NRNs and names generated from first search	*Prevalence study:* patients living within the study area on January 1st 2003 *Incidence study:* patients living within the study area at time of diagnosis between 1997-2006	Case records study and ascertainment of diagnosis	Application of the EMEA algorithm for classification

NRN: national registration number (Swedish: personnummer)

3.3 Diagnosis and classification

For diagnosis of vasculitis, patients should fulfil the entry criteria as shown in Table 14. A diagnosis of vasculitis can be done only if the patients fulfil all of the three criteria A, B and C. First, the patients should have clinical features that are either compatible or typical for vasculitis. The next criterion, B, is subdivided into 3 alternatives: histopathology (for such patient's clinical features *compatible* with vasculitis is sufficient), positive ANCA (in this case patients must have clinical features *typical* for vasculitis) and the presence of specific investigations strongly suggestive of vasculitis and/or granuloma. The third criterion C is that there should be no other inflammatory, infectious, malignant or drug-induced diseases which could explain the patient's clinical or laboratory presentation.

The classification algorithm (Figure 1) was then applied stepwise starting with the ACR CSS 1990 because it has the highest specificity. The next step in the algorithm is to apply ACR WG. Patients who did not fulfil ACR WG but (i) had histopathology findings compatible with CHCC WG, or (ii) histopathology findings compatible with CHCC MPA and surrogate markers for WG, or (iii) without histopathology findings but with surrogates markers for WG and a positive test for ANCA, were classified as WG. The next step in the algorithm is the application of CHCC definition of MPA. Patients with histopathology findings compatible with CHCC MPA and who lacked surrogates for WG were classified as MPA. Patients with no histopathology findings but with surrogates for renal vasculitis together with a positive ANCA test were classified as MPA. The CHCC definition for PAN was then applied; angiographic evidence of microaneurysms was considered to be highly suggestive for diagnosis in the context of clinical presentation of PAN.

Table 14. Entry criteria for the application of the EMEA algorithm

A.	Disease process characteristic of, or compatible with, a diagnosis of PSV
B.	Objective diagnostic measure supporting the diagnosis
1.	Histological proof of vasculitis and/or granuloma
2.	Positive serology for ANCA
3.	Specific investigations strongly suggestive of vasculitis and/or or granuloma
C.	No other diagnosis is more likely to account for symptoms and signs
1.	Malignancy
2.	Infection
3.	Drugs
4.	Secondary vasculitis
5.	Behçet's disease, Takayasu's arteritis, giant cell arteritis, Kawasaki's disease, cryoglobulinaemic vasculitis, Henoch-Schönlein purpura, anti-GBM disease*
6.	Pseudovasculitis
7.	Sarcoidosis and other non-vasculitic granulomatous disease

A, B *and* **C** *are all required for diagnosis.* * GBM: Glomerular basement membrane

Surrogate markers for WG: symptoms and signs suggestive of granulomatous disease affecting:

Upper airways: bloody nasal discharge and/or crusting for more than 1 month, or nasal ulceration; chronic sinusitis, otitis media or mastoiditis for >3 months; retroorbital mass or inflammation (pseudo-tumour); subglottic stenosis and saddle nose deformity/destructive sinonasal disease) and,

Lower airways: x-ray evidence of pulmonary infiltrates or cavitations present for more than one month, and bronchial stenosis.

Surrogate markers for renal vasculitis: proteinuria and haematurea with red cell casts, or 2 + haematurea and 2 + proteinuria on urinalysis.

Adapted from reference[15].

3.4 Data collection

For each patient included in the studies we used a predefined computerized database form to collect the patient's data. The following data were collected at time of diagnosis: demographics, time of onset of symptoms attributable to vasculitis, time of diagnosis, clinical features at diagnosis, blood pressure, results of relevant laboratory investigations (including blood count, c-reactive protein, urinary-sediment, s-creatinine level, ANCA, hepatitis serology), results of histopathology as well as relevant radiology or clinical physiology investigations. Data essential to estimate the VDI were collected from case records up to the date of point prevalence. In addition, available data on smoking habits at the time of diagnosis were extracted from case records.

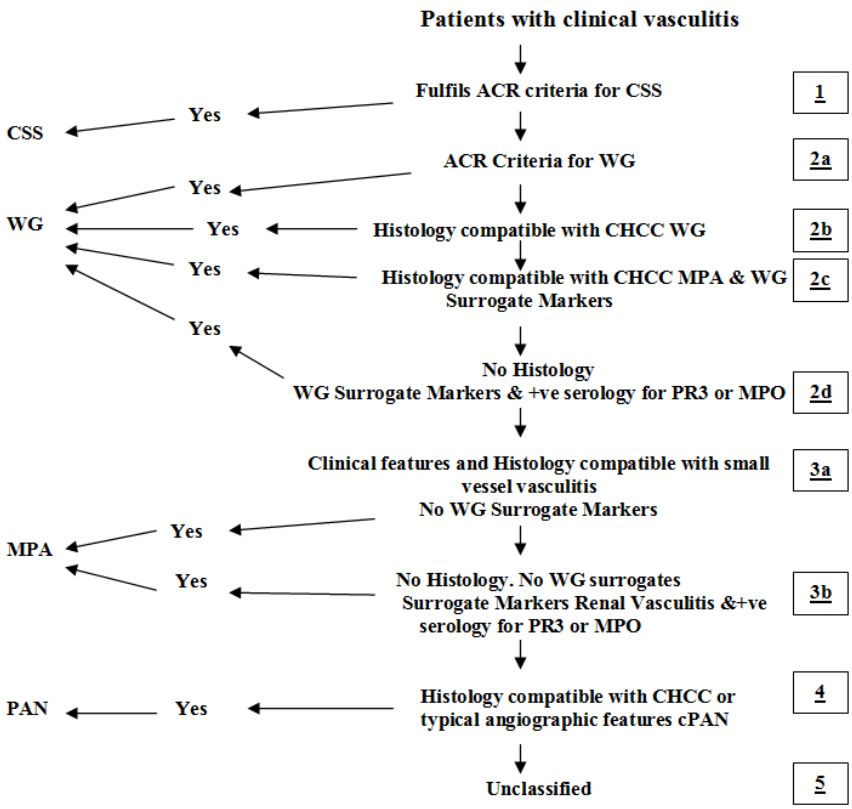


Figure 1. The EMEA algorithm

3.5 Assessment of organ damage

Irreversible organ damage was assessed for all patients in Paper II and IV using the vasculitis damage index (VDI). The time of assessment was the date of point prevalence (p.p.) which was January 1st 2003. The reviewed case records included clinical and radiological reports as well as reports from physiotherapists, occupational therapists, social workers and the available copies of the sick leave reports. In addition, relevant electrophysiological reports were collected if possible to register peripheral nerve

damage. In the absence of information on a given item of damage it was considered not be present. When no GFR measurements were available, we used the Modification of Diet in Renal Disease (MDRD) formula to estimate GFR [197] and let a filtration rate of 50ml/min/1.73m^2 represent a GFR of 50%, irrespective of age. In a similar fashion, we defined a dipstick value of ≥2+ to represent 24-hour proteinuria of more than 0.5g. We adhered strictly to the glossary and definitions of items of damage and the 3-month limit to register an item. A detailed description of each damage category is given in Paper II of this thesis. In Paper II, data on damage were analyzed for all 86 prevalent cases while in Paper IV data were analyzed only for the 77 patients for whom information on smoking habits was available in their case records.

3.6 Smoking data

Data on smoking habits (Paper IV) were collected retrospectively from available case records. These data were not available for 9 patients. Every effort was made to gather all information on smoking habits from doctors and nurse-notes as well as from the consultations and chest-x-ray referral letters. Patients were then stratified according to their smoking habits into two main groups: smokers (active and ex-smokers) and non-smokers (had never smoked). The assessment of organ damage was made using the VDI as described in Paper II.

Table 15. Vasculitis Damage Index (VDI)

Organ system Items of damage	**Definition**
1. Musculoskeletal	
Significant muscle atrophy or weakness	Demonstrated on clinical examination (not attributable to cerebrovascular accident)
Deforming or erosive arthritis	Deformities on clinical examination confirmed by radiographs (excluding a vascular necrosis); demonstrated on clinical examination and radiographs
Osteoporosis with fractures or vertebral collapse	By history confirmed by radiographs (excluding a vascular necrosis); ever since the onset of vasculitis
A vascular necrosis	Demonstrated by appropriate radiological techniques; ever since the onset of vasculitis
Osteomyelitis	Documented clinically, confirmed by radiographs and/or culture
2. skin/mucous membranes	
Alopecia	Major (e.g. requiring wig) chronic hair loss with or without scars, documented clinically
Cutaneous ulcers	Open sore on skin surface, excluding that caused by venous thrombosis
Mouth ulcerations	Recurrent crops or persistent mouth ulcers requiring therapy
3. Ocular	
Cataract	A lens opacity (cataract) in either eye documented by ophthalmoscopy
Retinal change	Any significant change documented by ophthalmoscopic examination; may result in field defect, legal blindness
Optic atrophy	Documented by ophthalmoscopic examination
Visual impairment/diplopia	Restricted eye movements (not due to nerve palsies), reduced visual acuity, double vision or tunnel vision
Blindness	Complete loss of vision in 1 eye
Blindness in second eye	At least 3 months after first event
Orbital wall destruction	Determined by plain radiographs or computed tomography scan
4. ENT	
Hearing loss	Any hearing loss due to middle ear involvement or to auditory nerve/cochlear damage, preferably confirmed by audiometry
Nasal blockage/chronic discharge/crusting	Difficulties with breathing through the nose and/or with purulent discharge and/or with crust formation usually requiring nasal lavage
Nasal bridge collapse/septal perforation	Saddle nose deformity and/or perforation of nasal septum
Chronic sinusitis/radiological evidence of bone destruction	Chronic purulent nasal discharge with sinus pain and/or radiologic evidence of sinusitis with or without bone destruction
Subglottal stenosis without surgery	Persistent hoarseness and/or stridor preferably confirmed by endoscopy and/or radiographs
Subglottal stenosis with surgery	Confirmed by otolaryngology surgeon
5. Pulmonary	
Pulmonary hypertension	Right ventricular prominence or loud P2 (confirmed by cardiologic investigation if appropriate)
Pulmonary fibrosis/cavity	According to physical signs and radiographs (confirmed by relevant tests if necessary); this may include patients who require pulmonary resection
Pulmonary infarction	According to CXR or ventilation/perfusion scan
Pleural fibrosis	According to chest radiographs
Chronic asthma	Significant reversible airways obstruction
Significant chronic breathlessness	Significant symptomatic breathing difficulties and/or shortness of breath without hard signs on radiographs or lung function test
Impaired lung function tests	Forced expiratory volume in 1 second or forced vital capacity ≤70%, or transfer coefficient for carbon monoxide (CO) ≤70%
6. Cardiovascular	
Angina/ coronary artery bypass	On history confirmed at least by electrocardiographic (ECG) changes

Myocardial infarction	On history confirmed at least by ECG changes or cardiac enzyme elevation; ever, since the onset of vasculitis
Second myocardial infarction	At least 3 months after first event
Cardiomyopathy	Chronic ventricular dysfunction documented clinically or on appropriate investigation
Valvular disease	Significant diastolic or systolic murmur confirmed by cardiologic tests if appropriate
Pericarditis	Symptomatic pericardial inflammation or constriction for at least 3 months or pericardiectomy
Hypertension	With a diastolic BP>95 mm Hg or requiring anti-hypertensive drugs
7. Peripheral vascular disease	
Absent peripheral pulse	In 1 limb, detected clinically
Second episode of absent peripheral pulse	In another limb, detected clinically, at least 3 months after first event
Absent peripheral pulses	In at least 2 limbs detected clinically
Major vessel stenosis	Such as carotid or renal stenosis, documented on Doppler echocardiography or angiography
Claudication	Exercise-related ischemic pain in peripheral large vessel present for at least 3 months
Minor tissue loss	Such as loss of finger tip pulp space, ever, since the onset of vasculitis
Major tissue loss	Such as the loss of digit(s) or limb(s), including by surgical resection, ever, since the onset of vasculitis
Second episode of major tissue loss	At least 3 months after first event
Complicated venous thrombosis	With persistent swelling, ulceration or clinical evidence of venous stasis
8. Gastrointestinal	
Gut infarction	Infarction or resection of bowel below duodenum; or of gall bladder, spleen or liver, ever, since the onset of vasculitis
Mesenteric insufficiency/ pancreatitis	Typical abdominal pain confirmed on angiography or enzyme changes
Chronic peritonitis	Typical abdominal pain and peritoneal irritation on clinical examination
Oesophageal stricture or upper gastrointestinal (GI) tract surgery	Documented endoscopically or radiologically; ever, since the onset of vasculitis
9.Renal	
Estimated or measured Glomerular filtration rate (GFR) <50%	By any locally used method
Proteinuria of >0.5 g/24 hours	According to locally determined method
End Stage Renal Failure	Failure of native kidneys for >3 months regardless of subsequent dialysis or transplantation
10. Neuropsychiatric	
Cognitive impairment	Memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance level, documented on clinical examination (e.g. short mental test score) or by formal neurocogntive testing
Major psychosis	Altered ability to function in normal activity due to psychiatric reasons. Severe disturbance of the perception of reality characterized by the following features: delusions, hallucinations (auditory, visual), incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized catatonic behaviour.
Seizures	Paroxysmal electrical discharge occurring in the brain and producing characteristic physical changes including tonic and clonic movements, and certain behavioural disorders. Only seizures requiring therapy for more than 3 months are counted as damage
Cerebrovascular accident (CVA)	CVA resulting in focal findings such as paresis, weakness, etc., or surgical resection for causes other than malignancy
Cranial nerve lesion	Cranial neuropathy, excluding optic nerve or sensorineural deafness
Peripheral neuropathy	Peripheral neuropathy resulting in either motor or sensory dysfunction

Transverse myelitis	Lower extremity weakness or sensory loss with loss of sphincter control (rectal and urinary bladder)
11. Other	
Gonadal failure	Premature secondary amenorrhea or azoospermia
Marrow failure	Leucopenia (WBC<4000/µl), or thrombocytopenia (platelets <140) or anaemia (haemoglobin<10) preferably confirmed by marrow aspiration
Diabetes	Requiring any type of therapy
Chemical cystitis	Persistent hematurea or shrunken bladder. This does not include acute hemorrhagic cystitis which should be scored in the ADR
Malignancy	Documented by pathology, excluding dysplasias
Other	Any feature considered by patient or doctor to be an important scar or consequence which has arisen since onset of disease

Adapted from reference [177]

3.7 Seasonal variation

The month of disease onset and diagnosis was registered. The four seasons were defined as follows: winter (December-February), spring (March-May), summer (June-August) and autumn (September-November).

3.8 Statistical methods

Statistical analysis was performed using the Statistical Package for the Social Sciences; SPSS for Windows (SPSS inc., Chicago, IL, USA). The differences between groups were compared using the non-parametric Mann-Whitney U-test and chi square ($\chi 2$) test when appropriate. The p-value of < 0.05 is considered to be significant.

In the first Paper, the **capture-recapture analysis** was applied to assess for the completeness of case finding. This kind of analysis was first used in studies estimating the size of fish and wildlife populations [198,199]. When using the capture-recapture technique to estimate the size of a population of birds, for instance, the first sample is captured for marking or tagging (captures) before releasing them back to their population and then another sample is taken to find the number of marked birds (recaptures) it contains. A number of birds are not caught by each sample (missing). It is possible to estimate the number of "missing birds" in both samples and providing an estimate of the total population by application of the capture-recapture analysis.

For the validity of the final estimates there are a number of assumptions to be verified. First, the population must be close with no changes during the investigation. Second, the birds should not loose their tag and should be possible to be re-identified (matched) properly. Third, they should have an equal chance to be caught by each sample ("equal catchability"). The fourth assumption is the independency between the sources, i.e., the likelihood of being captured in the first sample does not affect the likelihood of being recaptured in the second sample.

Capture-recapture analyses are now widely used to study the epidemiology of diseases. In situations where only 2 sources of case identification are used, the assumption of source independency is virtually impossible to be verified. In addition, the variable catchability is very likely. These 2 fundamental problems when applying a capture-recapture analysis to epidemiological studies utilizing 2 retrieval sources have been addressed and discussed in detail [132,200,201].

These problems can be overcome in settings where 3 or more sources of case identification

are used. This situation enables to perform log-linear modelling in order to identify and/or to adjust for potential violations of the assumptions of source independency and equal catchability. The source independency is usually verified by fitting the 2^n models (8 models in the case of 3-source capture-recapture analysis) to represent all possible 1st and 2nd order source-to-source interactions; the model with the best fit is chosen according to "goodness of fit" statistics. The assumption of "equal catchability" is identified by comparing the observed distributions of one or several demographic and clinical variables for the cases identified in each of the given source to the expected distributions. In case of statistically significant differences of case characteristic across the sources can be corrected for by implementing the corresponding variables in the log-linear model [132]. The Kaplan Meier method used to estimate **survival rates**. The analysis done in this study was based on overall mortality (irrespective of cause of death). The expected number of deaths was calculated by multiplying sex-, age- and calendar period-specific person years of follow up with corresponding rates for the entire Swedish population. The **standardized mortality ratio (SMR)** was obtained by dividing the observed number of deaths by the expected number. Ninety-five per cent confidence intervals (95% CI) were calculated assuming a Poisson distribution of the observed cases. A univariate analysis used to study possible potential predictors of reduced survival. A multivariate analysis was performed on variables with a statistically significant p-value in the univariate analysis. Data are presented as median and range if not otherwise stated.

The prevalence calculated using the number of a live patients living in our study area as the numerator and the population on the 2002, 31st, December as the denominator. The incidence estimates are calculated using the number of cases as the numerator and the mean population in 1997 and 2006 as the denominator. Patients were stratified in to younger and older age groups using the median age in respective study as a discriminator; at diagnosis in Paper III; and at p.p. in Paper II and IV.

3.9 Ethics

The studies were approved by the local Ethics Committee at the Faculty of Medicine, Lund University (LU 283-02).

4 Results

4.1 Prevalence of PSV (Paper I)

Eighty-six patients (49% female) living within the catchment area on the date of p.p. fulfilled the inclusion criteria. The point prevalence per million inhabitants on January 1st, 2003 was calculated to be 160 (95% CI 114-206) for WG, 94 (58-129) for MPA, 31 (11-52) for PAN, and 14 (0.3-27) for CSS. The overall p.p. of all PSV was 299/million inhabitants (236-362). The p.p. in the age group above 55 years (74.4 % of cases) was 837/ million (95% CI 632-1042). The sex distribution was relatively equal with a p.p. per million of 290 (202-378) for women and 309 (217-400) for men. The case completeness of retrieval sources was estimated by the capture-recapture analysis to be around 96%. Based on this analysis, we estimated the total number of PSV cases at 89.6 (95% CI 85-95), and p.p. for all PSV adjusted for incomplete case finding at 312/million inhabitants (247-376). There was a considerable overlap between retrieval sources in identifying cases with PSV. There were 37 (43%) cases identified by two sources and 17 cases (20%) were identified by all 3 retrieval sources (Figure 2). The most important retrieval sources were databases from the Department of Nephrology and Rheumatology together with Wieslab ANCA. These sources identified more than 93% of cases. Only 2 of the 6 cases not identified by this simplified retrieval were incidence cases diagnosed 1999 and 2002. No unique cases were identified at the primary care facilities or hospitals outside the study area, indicating that no or very few patients with vasculitis received their medical care outside the study area.

Table 16. The prevalence and incidence of PSV.
The point prevalence per million inhabitants estimated on January 1, 2003 (population 287 479).
The annual incidence rate (case/yr/million) in a study area with total population of 641 000.

Diagnosis	Point prevalence /million (95% CI) *No. of cases*	Annual incidence/million (95% CI) *No. of cases*
Wegener's granulomatosis	**160 (114-206)** *46*	**9.8 (7.4-12.2)** *63*
Microscopic polyangiitis	**94 (58-129)** *27*	**10.1 (7.7-12.6)** *65*
Polyarteritis nodosa	**31 (11-52)** *9*	**0.9 (0.2-1.7)** *6*
Churg-Strauss syndrome	**14 (0.3-27)** *4*	**0.9 (0.2-1.7)** *6*
All patients	**299(236-362)** *86*	**21.8 (18.2-25.4)** *140*

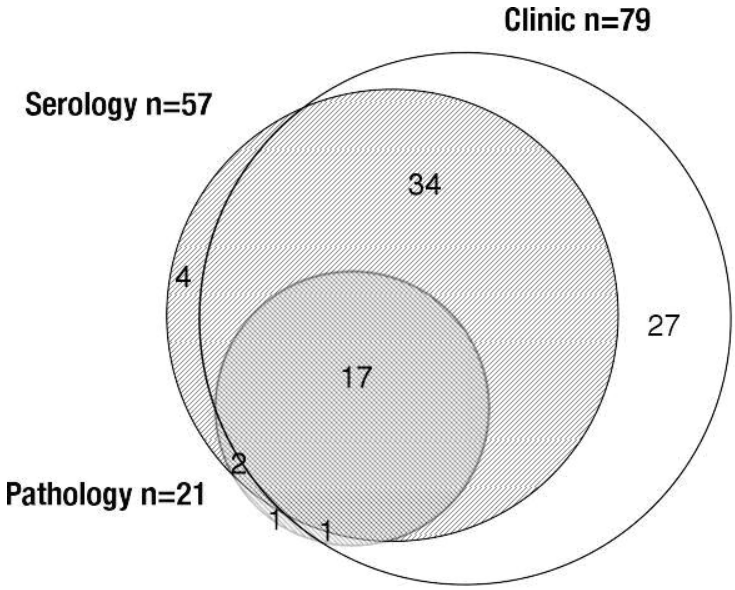


Figure 2. Overlap between the three retrieval sources used in the prevalence study: 32 cases (37%) were identified by a single source, 37 (43%) by two sources and only 17 (20%) were identified by all 3 retrieval sources

4.2 Annual incidence rates (Paper III)

One hundred and forty patients (52% female) were diagnosed with PSV between 1997 and 2006 in our study area. The patients were classified as follows: 63 WG, 65 MPA, 6 CSS and 6 patients as PAN. The annual incidence rates per million population were estimated to be 9.8 (95% CI 7.4-12.2) for WG, 10.1 (7.7-12.6) for MPA and 0.9 (95% CI 0.2-1.7) for each of CSS and PAN (Table 16). The annual incidence rate was 21.8/million (18.2-25.4) for all patients and 20.9 (17.3-24.4) for AASV. Table 17 shows the organ systems involvement at presentation in our patients.

The median age at diagnosis was 67.6 years (20-92) for all patients. The highest incidence rate was in the age group ≥75 years, 79.1/million (55.2-103). The incidence in the age group 35-54 years was significantly higher in women and the reverse was true for age group ≥75 years (Table 18). The incidence rates in the age ≥75 years group is significantly higher for MPA while in the age group 54-74 years WG incidence tends to be higher, though this difference was not statistically significant (Table 19 and Figure 3).

Table 17. Organ systems involvement according to BVAS at time of presentation in 140 patients with PSV diagnosed between January 1997 and December 2006.

Organ systems	All % (No.)	WG % (No.)	MPA % (No.)	PAN % (No.)	CSS % (No.)	p value*
General	84 (117)	89 (56)	83 (54)	83 (5)	33 (2)	*0.346*
Cutaneous	6 (9)	1 (1)	6 (4)	33 (2)	33 (2)	*0.184*
Mucous membranes/Eyes	7 (10)	13 (8)	3 (2)	0	0	*0.043*
ENT	38 (53)	73 (46)	5 (3)	0	67 (4)	*0.001*
Chest	41 (58)	59 (37)	28 (18)	17 (1)	33 (2)	*0.001*
Cardiovascular	5 (7)	3 (2)	5 (3)	0	33 (2)	*0.675*
Abdominal	9 (13)	3 (2)	15 (10)	17 (1)	0	*0.018*
Renal	70 (98)	48 (30)	98 (64)	50 (3)	17 (1)	*0.001*
Nervous	14 (19)	17 (11)	5 (3)	50 (3)	33 (2)	*0.020*

ENT: ear, nose and throat. BVAS: Birmingham Vasculitis Activity Score. P value*: between WG and MPA.

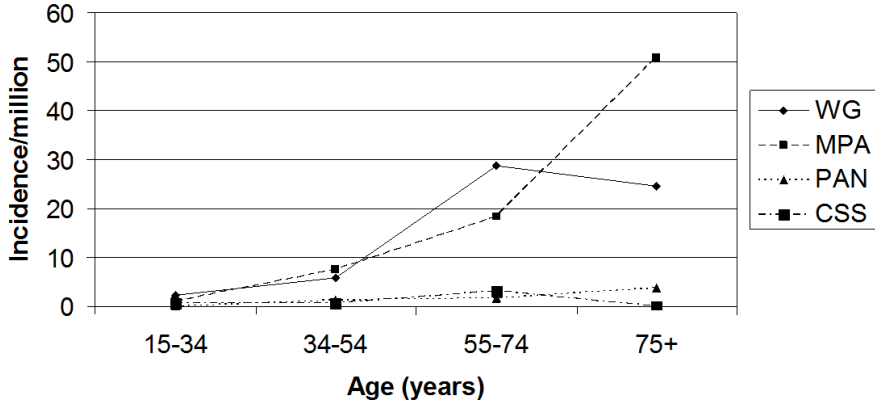
Table 18. Age-specific incidence rates in 140 patients with PSV.

Age groups	Total No. *Incidence/106 (95% CI)*	Men No. *Incidence/106 (95% CI)*	Women No. *Incidence/106 (95% CI)*	*P*
15-34 Years	7 *3.9 (1-6.8)*	4 *4.4 (0.1-8.8)*	3 *3.4 (0-7.2)*	*0,724*
35-54 Years	26 *15.7 (9.8-21.6)*	6 *6.9 (1.4-12.4)*	20 *23.5 (13.2-33.8)*	*0.005*
55-74 Years	65 *51.9 (39.3-64.5)*	34 *56.2 (37.3-75.1)*	31 *47.9 (31.0-64.7)*	*0.516*
≥ 75 Years	42 *79.1 (55.2-103.0)*	23 *117.4 (69.4-165.4)*	19 *56.7 (31.2-82.1)*	*0.016*

Table 19. Age-specific incidence rates in WG (no. 63) and MPA (no.65).

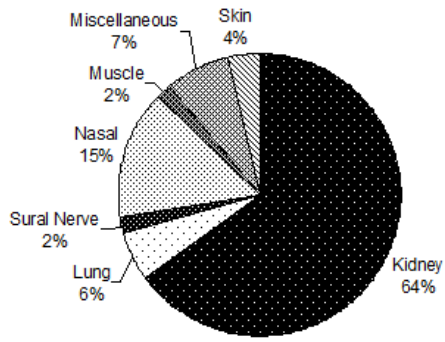
Age groups	WG No. *Incidence/106 (95% CI)*	MPA No. *Incidence/106 (95% CI)*	*P*
15-34 Years	4 *2.2 (0-4.4)*	2 *1.1 (0-2.7)*	*0.414*
35-54 Years	10 *5.8 (2.2-9.4)*	13 *7.6 (3.4-11.7)*	*0.531*
55-74 Years	36 *28.8 (19.4-38.1)*	23 *18.4 (10.9-25.9)*	*0.090*
≥ 75 Years	13 *24.5 (11.2-37.8)*	27 *50.8 (31.7-70)*	*0.026*

Figure 3. Age specific incidence in 140 patients with PSV (WG: 63, MPA:65, CSS:6 and PAN:6).



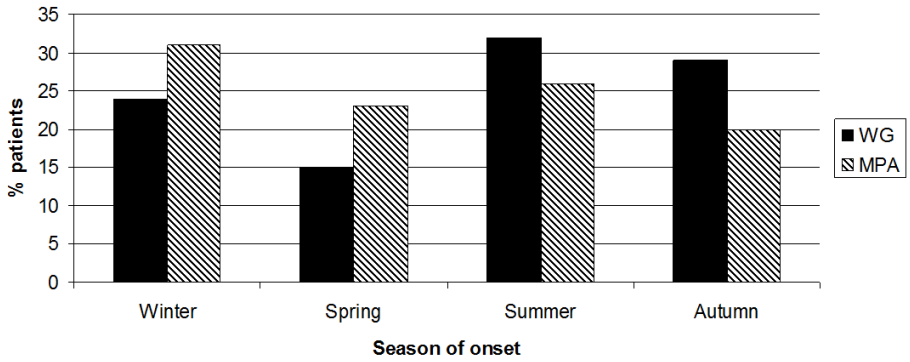
Tissue biopsies were obtained in 127 patients, with a diagnosis of vasculitis was supported by histopathology in 109 cases. Six patients presented with multiple positive biopsies. Figure 4 shows the distribution of organ biopsies that confirmed the diagnosis of PSV in our patients.

Figure 4. Diagnostic biopsies in 109 patients with PSV.
(For patients with multiple biopsies, only one is represented in the figure)



There were no statistically significant differences in the season of disease onset in our patients (Figure 5).

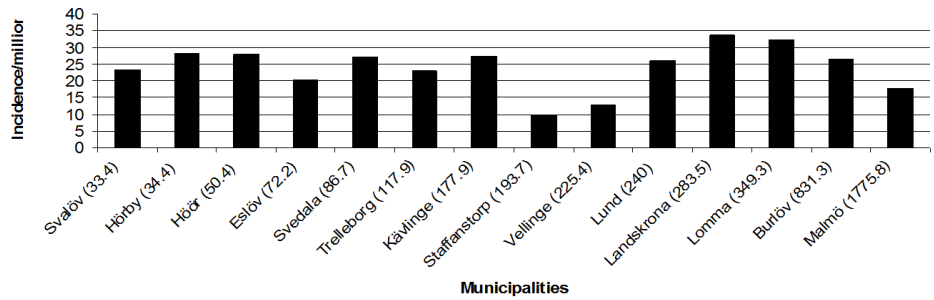
Figure 5. Seasonal variations at the onset of patients with WG (no. 62)* and MPA (65)



** Data for one patient was not available*

There was no significant change in incidence rates between 1997-2001 and 2002-2006. We could not identify any significant annual fluctuation in the incidence rates. When dividing the study area into two parts; the Mellersta Skåne district (the p.p. area) and the Sydvästra Skåne district; we found no significant differences in incidence rates.
There were no differences in incidence rates between areas with high vs. low population density (Figure 6).

Figure 6. Differences in the annual incidence rates of 140 patients with PSV according to population density (inhabitants/km²) in 14 municipalities in southern Sweden.

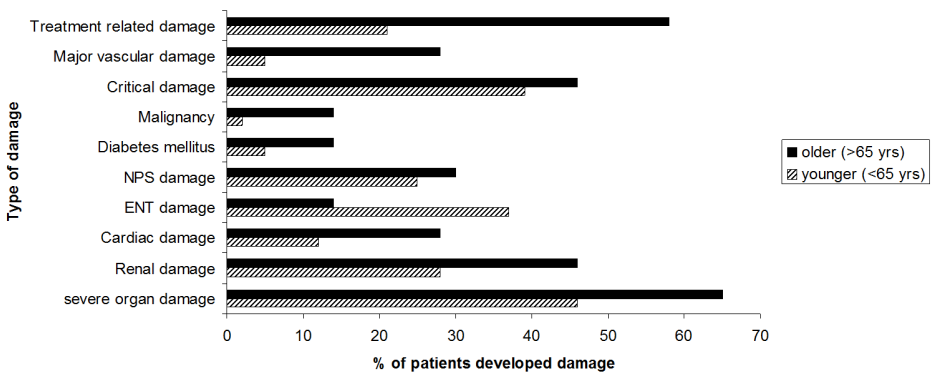


Numbers between brackets indicate inhabitants/km².

4.3 Damage estimates (Paper II)

Data to apply the VDI were available to all patients at the date of p.p. Data were registered up to January 1st 2003. Only eight patients (9%) were not assigned any item of damage. The median total VDI score was 3 (IQR 2-5) for all patients with a higher value for PAN and lower value for CSS [5 (IQR 2-6) and 1.5 (IQR 0.75-2.75)]. Forty-eight patients (56%) had developed severe organ damage. The most common damage was cardiovascular (51%), followed by renal damage (37 %), neuropsychiatric (28%), ENT (26%), and musculoskeletal (22 %). Older patients (>65 years) had a significantly higher total score of damage (p=0.005), higher rates of treatment related damage (p<0.001), major vascular damage (p=0.002) and malignancies (p=0.049), as compared with those below the age of 65 (Figure 7). The ENT damage was more prevalent in age group <65 years (p=0.013). The most common damage in WG was the ENT and cardiovascular damage (20 patients each, 43.3%) and in MPA cardiovascular and renal (17 patients each, 63%). Ischaemic heart disease (IHD: myocardial infarction, angina, coronary bypass surgery) had occurred in 11.6% of patients (MPA: 7.4%, WG: 13%). Hypertension was more common among MPA patients (60%) as compared with WG patients (33%), p=0.02. Similarly, renal damage was assigned to 17 (63%) patients with MPA compared with 12(26%) of WG; p=0.002. There was an almost complete separation between kidney and ENT damage; only 2 patients were assigned damage in both areas. Patients' assigned cardiac damage also had more severe damage in other organ systems than those without this kind of damage.

Figure 7. Selected organ damage estimated by the VDI in 86 patients with PSV stratified by median age, at the date of damage assessment, in to younger and older age group



The differences in damage between age groups were significant in: treatment -related damage (p<0.001), major vascular damage (p=0.002), malignancy (p=0.049), and ENT damage (p=0.013).

4.4 Smoking and organ damage (Paper IV)

Data on smoking habits were available for 77 patients (13 active smokers; 20 ex-smokers; 44 non-smokers). There were no differences between smokers and non-smokers in terms of median age at damage assessment, median time of diagnosis delay,

or median VDI score at final assessment. There were no differences in smoking habits between the two largest groups of patients [WG 40% smokers and MPA 45% smokers, p=0.672]. Smoking was more common at diagnosis among the men (61.5%) than the women (23.6%); p=0.001. ENT damage was recorded for a total of 17 patients (WG: 16; MPA: 1). The MPA patient with a VDI score in the ENT area had hearing loss. Among those patients who were active smokers at diagnosis, none had developed ENT damage. Accordingly, ENT damage was significantly more common in the non-smokers ($p<0.001$). There were no statistically significant differences between the smokers and the non-smokers in the prevalence of hypertension or other items of cardiovascular damage except for myocardial infarction (MI) which was significantly more prevalent among the smokers (p=0.048). Renal damage tended to develop more often among the smokers (45 %) as compared with non-smokers (33 %, p=0.17). This was more pronounced with severe renal damage and end-stage renal disease (ESRD) was statistically more common among current smokers as compared with non-smokers (p=0.04). WG patients who had developed renal damage, did not (with only one exception) exhibit damage in the ENT area. When comparing patients with renal damage with those who had developed ENT damage we found significant differences in smoking habits at diagnosis (smokers vs. non-smokers p=0.049). Patients with ENT damage tended to be younger and have longer diagnosis delay but these differences were not statistically significant (p=0.183)

4.5 Patient survival (Paper III)

The median time of follow-up for all patients from diagnosis to June 30, 2008 was 59 months (range 1-133). Forty-five patients (25 men) died during this follow-up period. The patients who had died during the follow-up had the following diagnosis: MPA 29 (64.4% of mortality cases); WG 14 (31.1%); and one patient in each of the PAN and CSS cohorts (2.2% each). For all the patients, absolute survival rates were 87.8% at 1 year, 71.6% at 5 years and 55 % at 10 years (Figure 8 A). The survival of patients with PSV was reduced compared with the Swedish population [SMR 2.77 (95% CI 2.02-3.71); 2.48 (1.60-3.65) for men and 3.27 (1.99-5.04) for women]. Survival for all PSV became worse with increasing age, $p<0.001$ (Figure 8 B). Not a single death was recorded during the follow-up time for the age group 15-54 years. There was no difference in survival rates between men and women (5-yr survival 67% for men vs. 75% for women, p=0.235). There was no difference in survival rate between patients with positive PR3-ANCA compared with MPO-ANCA. Reduced survival was found for patients with MPA compared with WG, and for those with renal involvement as well as for those without ENT involvement (Figure 8 C-E). The ENT involvement and a diagnosis of WG were associated with increased survival but when applying a multivariate analysis this effect was no longer significant. When studying only patients with WG there was no significant benefit from having ENT involvement (Figure 8 F).

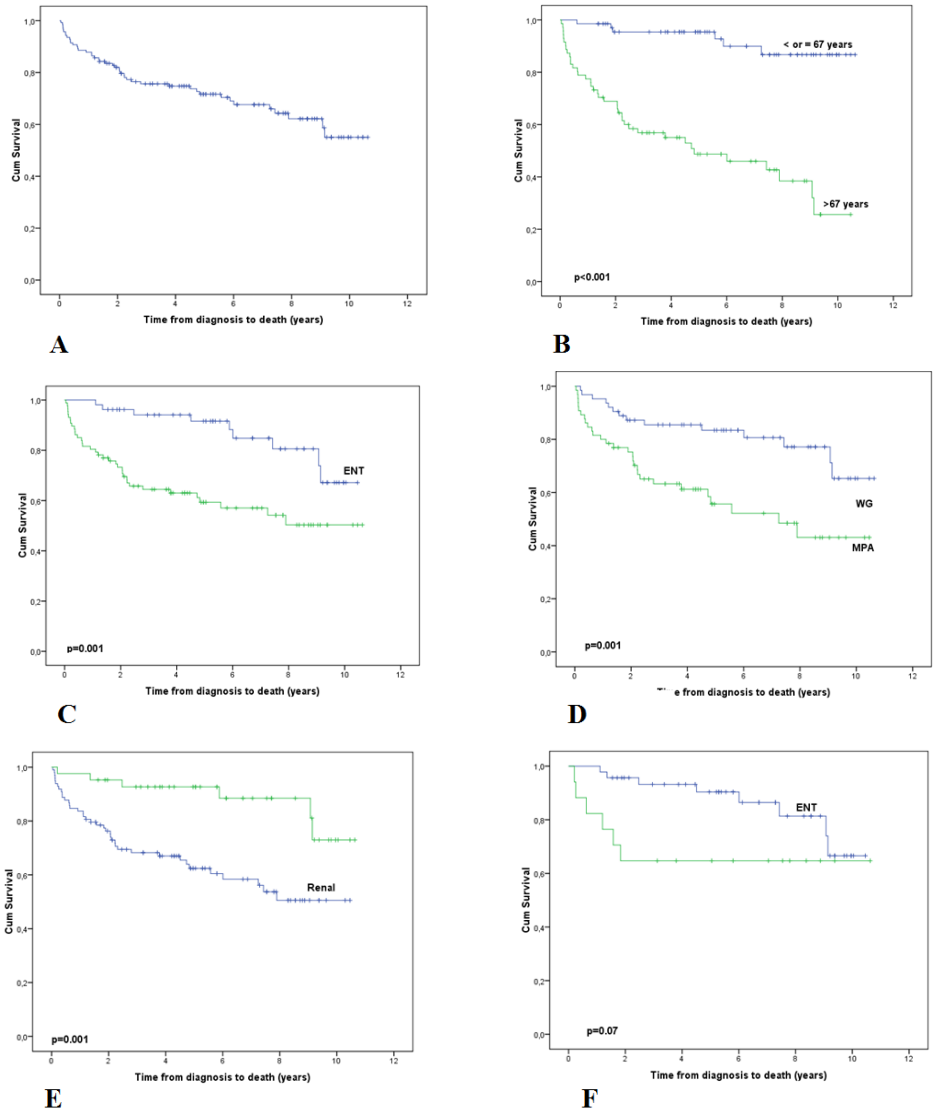


Figure 8. Survival curves. A: 140 patients with PSV. B: in younger (no. 69) compared with older patients. C: in patients with (no. 53) compared with those without ENT involvement at diagnosis. D: in patients with diagnosis WG (no. 63) vs. MPA (no. 65). E: in patients with (no. 98) compared with those without renal involvement at diagnosis. F: in patients with WG and with (no. 46) compared with those without ENT involvement at diagnosis. (Log Rank test has been used).

5 Discussion

5.1 The Epidemiology of PSV

5.1.1 The prevalence study (Paper I)

The prevalence figure for PSV of 299/million inhabitants (160 for WG, 94 for MPA, 31 for PAN and 14 for CSS) in our area is the highest ever reported. Available studies from other European countries and Australia provided prevalence of the PSV group ranging from 46 to 184 per million [116,117,129,132]. When looking individual diseases such as WG and MPA, the prevalence in our area is much higher than reported from other countries (Table 8). Possible explanations behind our high prevalence figures compared with other studies are: (i) good case retrieval, (ii) inclusion of high numbers of mild cases with PSV, (iii) differences in age distribution with high percentage of elderly people in our area, (iv) the use of the EMEA algorithm for classification of PSV, (v) good survival and (vi) a genuine high incidence rate of PSV in our area.

(i): The Swedish health care system and its accessible registries make our area very suitable for population-based studies of this type. And indeed, capture recapture analysis indicated that we identified above 95% of all cases of PSV. Other studies on the epidemiology of PSV resulted in much lower figures of case completeness, as this was reported between 73% and 76% in studies from Germany and France, respectively [122,132].However, even when inflating other studies with missing cases, our prevalence is still much higher than those reported by others.

(ii) Our study criteria are sufficiently restrictive that only patients with documented clinical diagnosis of PSV were included and all patients classified successfully in the four disease phenotypes studied according to the PSV definitions used in these studies. "Borderline" cases were not included. Furthermore, our findings in Paper II counteract the possibility of including "mild cases" in our study since only 9% of our patients were not assigned any kind of organ damage. This figure is quite comparable with other reports [177,179]. In addition, more than 50% of the cases suffered severe damage with a total VDI score of ≥ 5, ≥ 3 systems damage and/or ≥ 1 critical damage.

(iii) The age distribution in our area is fairly similar with European countries where epidemiological studies on the PSV have been carried out, such as Norway, Spain, UK, France and Germany and people ≥ 65 years constitutes about 15%-17% of the general population[202]. Difference in age distribution can not explain the high prevalence figures.

(iv) The EMEA algorithm has very little impact on the total prevalence figure. It does mainly effect the differentiation between WG, MPA and PAN.

(v) Prevalence is, by definition, a direct consequence of the patient's survival. In our area, the vast majority of patients is treated and followed at university clinics with highly specialized care. The survival rate in our area is good and comparable with other studies (Paper III), in spite of the fact that the median age of our patients is nearly 10 years higher than in most other case series[55,57,58,61,174,175]. In addition we did not have a single mortality in patients younger than 55 years. We therefore believe that the survival factor is an important explanation for the higher prevalence figure in our area.

(vi) The incidence of PSV in our area is comparable with the reported rates from many

European countries (see section 5.1.2), and can only explain a minor part of the high prevalence figure in our area.
In summary, we believe that the combination of good retrieval methods and good survival are the most important factors explaining why the prevalence figure in our area is higher than in other regions of the world.

5.1.2 The incidence study (Paper III)

The overall incidence rate of PSV in our area is marginally higher than that found in other European countries [115], but much higher than the incidence rates reported recently from Australia [117]. However, an important difference from other European studies is the nearly equal incidence of WG and MPA in our area, findings that clearly contradict the north-south hypothesis on the epidemiology of WG and MPA in Europe [115]. The increasing incidence with age has been previously reported in other studies with a peak incidence in the age group ranging between 55-74 years [54,114,116,137]. However, we found an increasing incidence rate even beyond the age of 75 years. In our study, this increment seems to be driven by the MPA diagnosis with an incidence peaking above the age of 75 years (see Table 19 and Figure 3). The incidence rate of 0.9/million for PAN in our area is lower than the figures reported by other studies using the ACR criteria 1990 (Table 7). The entry criteria and classification algorithm used in our study were more restrictive than the ACR PAN. However, in the case of CSS, our low incidence rate cannot be explained by a classification issue since in all these studies the ACR CSS criteria were applied.
We believe that there is a minimum of selection or referral bias in our study. The healthcare system in Sweden is accessible to all. The age of the patients does not have a major impact on the decision and intensity of the diagnostic work-up. Hospital-based cohorts tend to report a lower peak age as elderly patients are less prone to be referred to tertiary care centres.
Our study was not able to address the possible differences in incidence of PSV between rural and urban areas. However, we did not find differences in incidence rate between areas with different population densities. Other studies have indicated a lower prevalence of WG in large cities as compared to small communities in rural areas [117,130,132]. However, newly presented data from the UK was unable to confirm the findings that AASV is more common in rural areas [203].
We did not find any seasonal variations of the onset of PSV. Our results will add to the accumulated evidence of the absence of such variations in PSV.

5.2 The outcome of the PSV

5.2.1 Patient survival (Paper III)

We present survival data on patients with PSV from a well-defined stable homogeneous population. In our study, the 1-, 5-, and 10-year survival for WG was 95%, 83% and 65% respectively and for MPA was 80%, 55% and 43%. These figures are comparable with other studies on survival in patients with WG and MPA (Tables 10 and 11). The present study show a reduced survival rate for PSV compared with the general Swedish

population. Our findings support results from previous studies reported on the SMR in patients with PSV [55,56,144,163,165]. During the follow-up in our study, there was no single death in patients below 55 years at diagnosis, adding to the evidence of the impact of higher age on mortality rates in PSV. In addition to high age at diagnosis, high serum creatinine at presentation was also a predictor of reduced survival, which is in agreement with other studies [56,58,61,165]. Previous reports on WG showed that the presence of ENT involvement was associated with better survival [57,58,175]. These findings were also supported by a new study from South Australia showing a trend towards better survival for patients with upper respiratory tract involvement [134]. We also found a better survival for PSV patients with ENT involvement; however, in our study this difference was not significant when the analysis was restricted to WG. There was a better survival for WG compared to MPA, which explains the higher prevalence for WG in our area despite equal incidence rates. The logistic regression analysis indicates that differences in survival rates can be largely explained by high age and the presence of renal involvement rather than specific diagnosis. For similar reasons, studies including only patients with renal involvement within the AASV group did not find differences in the mortality rate between WG and MPA [64,176].

5.2.2 Damage estimates (Paper II)

In Paper II we present a cross sectional study that aimed to estimate the extent and pattern of irreversible organ damage in patients with PSV from a point prevalence perspective for patients retrieved from a defined geographical area. We found that damage is still an important clinical problem in our patients, especially at high age. The population-based approach was a major strength of this study. Studies from larger cohorts originating from tertiary centres or clinical trials usually have referral bias. We believe, therefore, that the patients in our study are representative of vasculitis patients on the individual level and relatively well mirror the fate of "typical" vasculitis patients in other parts of the industrialized world. However, this point should not be a major potential misinterpretation, as the exclusion of non-survivors in our study is not a selection bias since the study by definition is designed to address damage in prevalent cases. Consequently, this is not a cohort study and it does not allow for the study of any predictors of damage and mortality. Therefore, the results reported here cannot be directly comparable with other cohort studies using the VDI in the assessment of organ damage [61,179].

Cardiovascular damage was the most common in our patients. Hypertension occurred in 41% of the patients and was more common in MPA probably because of higher prevalence of renal involvement in these patients. In a recently published Danish study on WG, there was a large number of patients who experienced an increase of both early and late cardiovascular events due to IHD [204]. The mechanisms behind the increased risk of IHD in WG were unclear but may include disease-specific and therapeutic factors. Both active inflammation in WG and its therapy with high dose corticosteroids might enhance the development of the atherosclerosis. Patients receiving high dose CYC had a higher risk of IHD[204]. Similarly, our patients who were assigned cardiac damage, including IHD, have had significantly higher total VDI scores than those without this kind of damage, indicating more serious disease in those patients.

We found that damage is more common in the elderly. This is quite obvious and no new

finding, but might indicate the difficulty of treating elderly patients who suffer serious diseases especially when cytotoxic and immunosuppressive agents are used. However, the findings of complete dissociation between ENT and renal damage and cardiac damage are interesting and add to the evidence of the "good prognosis" in the presence of ENT involvement in WG [58,175]. In addition, the very recently revised FFS showed that the presence of ENT symptoms had a positive effect on the survival [171]. The question to be raised is whether WG is one disease with two aspects; the granulomatous and the vasculitic; or it is two different diseases, with or without systemic involvement. These two diseases or "aspects" of disease usually have much in common, making the distinction between them early on at disease onset difficult. It is not before a long time of follow-up that they crystallized into two different diseases: WG vs. MPA or localized vs. systemic/renal WG.

Because of the diversity of clinical manifestations and mild disease presentation in some patients, especially in WG, patients can be evaluated for a long time for infectious or malignant diseases before they are referred to rheumatology or nephrology units. The median time for diagnosis delay in WG has been reported to be between 2-17 months [52,56,57,119,122,175,205]. There is, however, a trend towards a shorter diagnosis delay as recently made evident in a study from Finland [205], probably because of increased awareness and improved diagnostic work-up during the last years. However, unfortunately this seems, at least in our study, not to have had a major impact on the evolution of damage except for patients with ENT damage that have had a longer diagnosis delay.

Detailed data on the treatment given to each patient were not collected in our study. Our patients have been diagnosed over a long time period during which the therapy of vasculitis has undergone successive development. Differences in therapies depended on the period in which the diagnosis was given. This is a factor that would bias the results of the influence of treatment on organ damage. Data on the role of therapies in the development of damage have been addressed previously [61,179]. As mentioned above, a cohort study is best suited to answer the question if the type of therapy has had a major impact on the extent of damage.

The findings presented in this study also show, from another perspective, that vasculitis patients are big consumers of the healthcare system and there is a need to review the resources provided for the care and research of vasculitis. Even if our study was not designed or aimed to address the issue of disease burden, the results can present crude information to the researchers and health planners about the heavy load on resources required for the care of PSV patients.

5.2.3 Smoking and organ damage (Paper IV)

In Paper IV we present a novel finding concerning the negative association between cigarette smoking and the development of irreversible damage in the ENT area in patients with PSV. The aim of our study was not to describe a causative or protective association between smoking and PSV and/or its organ damage. Until recently, there were no data on the relationship between smoking and the outcome of PSV. A German study published in 2005 showed a significantly lower prevalence of smoking in patients with AASV than in the general population [194]. The reason for that was unknown; according to the authors possible environmental factor(s) associated with non-smoking might influence

the development of vasculitis. According to Statistics Sweden, the smoking habits in the Swedish population are declining; 31.4% of the population smoked daily in 1980 and in 2006 this figure had dropped to 14.8% [196]. Furthermore, smoking is far less common among people working within farming in Sweden (8.9%) compared with all other professions put together (23.4%), and this figure is much lower for people aged ≥75 years (5%). Accordingly, in view of the German study and the previously published data on the association between PSV and farming [138], together with our results of high incidence in older people; one might speculate on one of the causes of the changing incidence of PSV. Now putting these facts together, the results could indicate that the incidence of PSV is increasing; moreover, it should be more common among farmers and in people over the age of 75. A case-controlled study including a large population designated to answer these questions is necessary and should give very interesting results.
The patients who developed irreversible ENT damage according to VDI were exclusively non-smokers (never-smoked). The association of smoking with cardiovascular and renal damage was not a surprise as this association is well-known from the medical literature. However, the importance of our finding of a negative association between smoking and the development of ENT damage is, in addition to being new, is that it adds to growing evidence of the separation between AASV involving the ENT (granulomatous) from systemic disease (vasculitis), as discussed above.
In our study, about 92% of the ENT items registered in non-smokers were confined to the nasal area and sinuses, while the only item of ENT damage registered in one ex-smoker was hearing loss. The distribution of damage even within the ENT-area further pointed to local "anti-inflammatory" probably being a direct effect of cigarette smoke (nicotine mediated?) on the nasal mucosa. This possible local effect may ameliorate symptoms and signs in the nasal area and diminish or prevent the development of damage there. The other possible explanation is that patients with systemic disease presented earlier and accordingly received their effective therapy prior to the development of further damage. In our study, patients with developed ENT damage have had longer duration of symptoms prior to diagnosis than patients who escaped this kind of damage. From clinical experience, WG patients with features limited to the ENT area may seek medical attention and receive two or maybe three courses of antibiotics before the diagnosis of WG can be made. While patients with more severe systemic disease with symptoms from lungs and kidneys have a shorter diagnosis delay usually receive immunosuppressive treatment early on in the course of their diseases. Studies demonstrated that smoking exhibits some modulating effect on inflammatory conditions in mucous membranes such as in Behçet disease [193]. However, a Japanese study, published recently, demonstrated that cigarette smoking, in the presence of HLA-B51, but not alone, has been shown to be a risk factor in the development of chronic progressive neuro-Behçet disease [206]. Similarly, this kind of synergistic interaction between an environmental factor (cigarette smoking) and genetic predisposition (HLA type) proved to be a risk factor for the expression of anti-CCP antibodies associated with the development of RA [207].
Apart from the differences in smoking habits, we were unable to show any statistically significant differences in age at diagnosis, gender, disease duration or ANCA positivity between patients with and without ENT damage in WG. The exact mechanisms involved in the interaction of smoking and the development of damage in the ENT area in our patients is unclear. A prospective study on a large cohort of patients may help to solve this conundrum.

6 Practical implications

The results presented in this thesis may have some implications for the care of patients with systemic vasculitis. We have developed an epidemiological methodology capable to identify nearly 95% of patients with PSV. This will facilitate future studies in establishing cohorts for long-term outcome studies as well as for longitudinal studies of changes in incidence rates. Our studies have added considerable knowledge on the epidemiology of PSV in general and especially in Sweden and established an important start to continue a cohort of vasculitis patients for future outcome studies. We showed that vasculitis care in our area is of high quality; both in diagnostic facilities and outcome; and it is in many aspects comparable to other countries in terms of substantial experience and tradition for vasculitis research. The awareness of physicians of PSV may be further improved, hopefully resulting in improving the outcome for patients. Our data on organ damage may be used as a key argument for demanding better resources for the highly specialized vasculitis care. Our study on organ damage was not designed to give an accurate estimate of the burden of PSV in any specific manner. However, it has been demonstrated that patients with these diseases are heavy consumers of expensive healthcare facilities, such as dialysis and transplantation, and hopefully this will help to improve the healthcare of these patients as well as aid the researchers in the field of vasculitis to convince the healthcare planners and fund providers to prioritize this field of research. Our incidence results showed increasing incidence with age, and it is therefore of importance to consider these diseases in elderly patients presenting with “unclear” systemic disease or “therapy resistant pneumonia”.

7 Strengths and limitations

The strengths of these studies lay in being population-based. Patients included in these studies are retrieved from a well-defined homogeneous stable population which is ideal for epidemiological studies. The response rate from departments and hospitals asked to contribute with lists of patients assigned the PSV diagnosis was 100%. We have had unlimited access to all case records of potentially eligible patients with the exception of a very small number of patients whose records were not found. There were no referral or selection biases in our study; an important shortcoming in studies from tertiary centres. The reliability of the matching criteria used in these studies was 100%. The Swedish national registration numbers are extremely useful for such studies. The widely used, comprehensive and accessible registers used in the healthcare in Sweden make case retrieval and case identification easy and time saving. Finally, the work done by the vasculitis network in Lund and Malmö since it was established gave the network wide acceptance among other physicians in our area and helped to increase their awareness of ANCA associated vasculitis and vasculitic diseases in general. Finally, our capture-recapture estimates show a very high case completeness indicating that our figures are the nearest to real incidence and prevalence figures a modern epidemiologic study can achieve.

The limitations of these studies include a number of important items, such as data collected retrospectively are by their nature incomplete. We were not being able to estimate the disease activity retrospectively using the BVAS. The BVAS assessment in a retrospective way may be unreliable since many aspects in BVAS need to be done at the time point of assessment of disease activities. For the same reason, in the smoking study, we could not find data on all the patients which is why these patients were omitted from the statistical analysis. We have not studied causes of death in our patients and are therefore not able to address the contributions of vasculitis diseases or its treatment to mortalities. The population of the study area was also relatively small, especially when reporting on CSS and PAN. The duration of the incidence study was not long enough to enable a more reliable study on the annual or temporal fluctuation of incidence rates.

8 Conclusions

1. Using multiple retrieval sources is very helpful in identifying the majority of patients with PSV. The case completeness in our study estimated by the capture-recapture technique was 96%.
2. We found that the EMEA classification algorithm easy to use and feasible and appropriate for future studies.
3. The simplified search method using clinical databases from rheumatology and nephrology departments together with ANCA analysis by ELISA gave the best yield, identifying 93% of cases.
4. The prevalence of PSV in our area is the highest reported so far
5. The incidence of WG is equal to that reported from other European countries but the incidence of MPA is substantially higher than that reported from the northern countries.
6. Our results clearly challenge the so call north-south hypothesis in the epidemiology of PSV.
7. There were no seasonal variations or annual fluctuations in onset of PSV.
8. Mortality is worse in patients with MPA than WG, possibly due to differences in the incidence of renal involvement and higher age of the MPA patients.
9. Overall PSV survival is reduced compared with the general Swedish population.
10. High age and renal involvement are major predictors of survival, while ENT involvement seems to have some positive effect on survival rate.
11. Only a few patients escape organ damage in spite of the availability of remission induction and maintenance treatment and the relatively short time from onset to diagnosis.
12. The damage was more evident in older patients.
13. There was a nearly complete dissociation between renal and ENT damage; a finding that raises the question of the possibilities of differences in pathogenesis of WG in limited vs. systemic disease.
14. Smoking affects the pattern of damage in patients with PSV. ENT damage occurs exclusively in non-smokers while smokers developed more renal and cardiovascular damage.

8.1 Future studies

Long-term follow-up of the existing cohort of our patients to study predictors of outcome both in term of survival and morbidity

Case-controlled studies to address issues on aetiology and pathogenesis of PSV.

Research projects; involving patients with vasculitis, dealing with some form of education or information or vasculitis schools are interesting.

9 Popularized summary in Swedish

Populärvetenskaplig sammanfattning på svenska

Vaskulit betyder blodkärlsinflammation. Systemiska vaskuliter är ett samlingsnamn för en grupp sjukdomar kännetecknas av inflammation av blodkärl i olika organ i kroppen. Sjukdomsbilden och konsekvenserna av olika vaskulitsjukdomar varierar beroende på vilket kärlområde som drabbas. Utbredning och intensitet av inflammationen kan orsaka olika symptom med varierande klinisk bild som kan sträcka sig från en godartad till allvarlig livs- eller organhotande. Vaskulit som engagerar ett organområde exempelvis huden kallas för begränsad vaskulit, medan en vaskulitsjukdom som involverar flera organ såsom njurar, lungor och nervsystemet kallas för systemisk vaskulit. Systemiska vaskuliter kan vara delfenomen i en annan sjukdom såsom reumatisk eller infektionssjukdom men kan också orsakas av ett läkemedel, och i alla dessa fall kallas för sekundära vaskuliter. Vaskulitsjukdomarna utan samband med annan bakomliggande sjukdom kallas för primära vaskuliter som kan definieras efter storleken av det engagerade kärl; till små-, medelstora, och storkärlvaskuliter.

Primära systemiska vaskuliter betraktades under många år som sällsynta och hade hög mortalitet innan man började behandla dem med högdos kortison och cellgifter. Sedan slutet av 80-talet finns serologiska test kallade ANCA (=anti-neutrofila cytoplasmatiska antikroppar), som har underlättat diagnostiken.

Wegener's granulomatosis (WG), mikroskopisk polyangiit (MPA), Churg-Strauss syndrom (CSS) och polyarteritis nodosa (PAN) är primära vaskuliter engagerar små och medelstorkärl och har många gemensamma kliniska, patologiska och laboratoriska karaktärer. På grund av stark association till ANCA kallas WG, MPA och CSS tillsammans som ANCA associerade systemiska vaskuliter (AASV). Polyarteritis nodosa (PAN) är en ovanlig vaskulitsjukdom engagerar medelstora kärl. Tillskillnad från MPA, har patienter med PAN ingen inflammation i njurvävnad (så kallad glomerulonefrit) och ingen ANCA. Dessa 4 sjukdomar studeras ofta tillsammans och många författare betraktar dem som en group; vi härefter refererar till de tillsammans som en grupp, primära systemiska småkärlsvaskuliter (PSV). Under de senaste åren, flera studier från olika delar av världen visade ökad incidens (uppkomst) och prevalens (förekomst) av PSV. Kombinationen förbättrad diagnostik, tillgång till bättre behandling och förbättrad överlevnad diskuteras ofta som möjliga förklaringar till den senaste ökning av incidensen och prevalensen av PSV.

Syften med denna avhandling var att (i) studera den årliga incidensen (uppkomst) och prevalensen (förekomst) av PSV i ett definierat geografiskt område i södra Sverige, (ii) studera omfattningen av permanenta organskador hos våra patienter med PSV vid bestämd tidspunkt, (iii) studera patients överlevnad och de olika faktorer som kan ha påverkan på det och (iv) studera sambandet mellan rökvanorna och utvecklingen av organskador hos patienter med PSV.

I **delarbete I** gjordes en omfattande sökning i olika register och databaser för att identifiera patienter som har fått diagnoser inom PSV gruppen och som bor i ett definierat geografiskt område (mellersta Skånes sjukvårdsdistrikt). Vi sökte i såväl journaldatabaser från sjukhus och vårdcentralen, och i diagnostiska databaser från olika laboratorier. Totalt fann vi 86 patienter bodde i mellersta Skånes distrikt 2003-01-01 och uppfyllde studiekriterierna . Könsfördelningen var jämn (44 män, 42 kvinnor). Median åldern

vid punkt prevalensdagen, 2003-01-01, var 65 år. WG var den vanligaste sjukdomen, 46 patienter, vi fann också 27 med MPA, 9 med PAN och 4 patienter med CSS. Punktprevalensen för all 4 sjukdomarna i PSV gruppen var 299 fall per million invånare (WG 160; MPA 94; CSS 14 och PAN 31). Ett särskilt beräkningssystem (så kallas capture-recapture analysen) applicerades till vår metod för att se hur bra den var för att identifiera patienter med PSV som bor i vårt område. Beräkningen antydde att vi bara hade ”missat” kring 3 personer. Enligt denna studie, finns det cirka 350 personer i Skåne som lever med dessa sjukdomar. De här sjukdomarna kan ha allvarliga konsekvenser och påverka många organ i kroppen, inte minst njurarna som kan få svåra skador att dialysbehandling blir nödvändigt. I **delarbete II** studerade vi omfattningen av permanenta organskador som drabbat våra patienter med PSV. För att uppskatta mängden organskador använde vi en skadeindex som dokumenterar omfattning av permanent organ skada; vasculitis damage index (VDI). I denna skadeindex registreras samtliga skador som uppstått sedan sjukdomen startade. Vi fann att organskador var mycket vanliga hos våra patienter och endast 9% var helt fria från skador. De valigaste organskadorna var hjärtkärlsjukdomarna, njurskador, neuropsykiatriska och öron-näsa-hals (ÖNH)-skador. Dessutom hade 9% av patienterna utvecklat diabetes och 8% diagnostiserats med cancersjukdom. Vi fann att våra yngre patienter hade mer ÖNH-skador medan njurskador var vanligare hos de äldre. Vi hittade i det närmaste total separation mellan ÖNH-skador or njur-, samt hjärtskador (hjärtinfarkt, angina och genomgång kranskärlsoperation), bara två av 22 patienter med ÖNH-skador hade utvecklat njurskada och ingen hade hjärtskada.

I **delarbete III** studerade vi den årliga incidensen (antal patienter som insjuknar varje år) av PSV i ett område med cirka 641 000 invånare. Studietiden var en 10-årsperiod mellan januari 1997 och december 2006. Totalt hittade vi 140 nyinsjuknande patienter (73; 52 % kvinnor) med PSV (WG:63, MPA 65, CSS och PAN 6 patienter var). Median åldern vid diagnosen var 68 år. Den totala årliga incidensen för hela PSV gruppen var 21/ million invånare, och för de enskilda sjukdomarna: 9.8 för WG, 10.1 för MPA och 0.9 för CSS och PAN var. Vi hittade ingen skillnad i incidensen mellan kommunerna med höga respektive låga befolkningstäthet, och inte heller fanns signifikanta säsongvariationer vid sjukdomsdebut. Vi fann också att incidensen av PSV ökar med åldern med högsta ålders specifika incidens var bland personer som är 75 år och äldre (79.1/ million).

Under en uppföljningstid mellan januari 1997 och 30 juni 2008 dog fyrtio-fem patienter. Den 1-, 5-, och 10-års överlevnad för hela PSV gruppen var 87.8%, 71.6 % och 55 %. Resultat var i stort sätt jämförbara med studier från övriga länder. Vår studie visade en tydligt ökad dödlighet hos patienter med PSV jämfört med den svenska befolkningen. Personer med PSV hade 2.77 gånger högre risk att dö jämfört med bakgrundbefolkning. Överlevnad var sämre för patienter med MPA än WG, vilket förklarar varför vi hittade dubbelt så många WG patienter i studie 1, fast lika många patienter insjuknar varje år i MPA och WG.

I **delarbete IV** studerade vi sambandet mellan rökvanorna och utvecklingen av organskador enligt VDI. Data om rökvanor fanns registrerade för 77 patienter i studie 1 (33 rökare och 44 icke rökare). Organskador registrerades enligt VDI vid punktprevalensdagen 2003-01-01. Rökning var vanligare hos män men det var ingen skillnad i rökvanor medan patienter med MPA och WG diagnoser. Vi presenterade ett unikt och helt nytt fynd: patienter som utvecklade näs别skador hade aldrig rökt, medan rökare hade en större tendens till både njur- och hjärtpåverkan. Hjärtsjukdomar framför allt hjärtinfarkt och njursvikt som kräver dialysbehandling var vanligare hos rökare än

icke-rökare.

Sammanfattningsvis har de studier som ligger till grund för den här avhandlingen visat att (i): vi har fler patienter i livet med PSV (Wegener's granulomatosis, mikroskopisk polyangiit, Churg-Strauss syndrom och polyarteritis nodosa) i mellersta Skåne än vad man funnit någon annanstans i världen, (ii): trots detta var antalet nyinsjuknade varje år jämförbart med vad som rapporterats från andra länder (iii): dödligheten var i nivå med vad som presenterats i behandlingsstudier, trots att våra patienter var betydligt äldre. (iv) hög ålder vid diagnos och svårt njurengagemang ökade risken att dö (v): organskador är mycket vanliga hos patienter med PSV och att bara några få patienter hade helt sluppit alla former av skada tillföljd av sin sjukdom, (v): det finns samband mellan rökning och utveckling av organskada där rökning har en viss skyddande effekt mot utveckling av skador i näsan.

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