Mortality and causes of death across the systemic connective tissue diseases and the primary systemic vasculitides

Torhild Garen[1], Karoline Lerang[1], Anna-Maria Hoffmann-Vold[1], Helena Andersson[1], Øyvind Midtvedt[1], Cathrine Brunborg[2], Karin Kilian[1], Birgir Gudbrandsson[1], Ragnar Gunnarsson[1], Gudrun Norby[1], Asad Chaudhary[1], Jørn Thoen[1], Karin Øien Forseth[1], Kari Fresjar[1], Øystein Førre[1], Margaretha Haugen[1,3], Hans-Jacob Haga[1], Jan Tore Gran[1], Inge-Margrethe Gilboe[1], Øyvind Molberg[1,4] and Øyvind Palm[1]

Abstract

Objectives. Studies assessing relative mortality risks across the spectrum of systemic inflammatory rheumatic diseases are largely missing. In this study, we wanted to estimate standard mortality ratios (SMRs) and causes of death in an ethnically homogeneous cohort covering all major CTDs and primary systemic vasculitides (PSVs).

Methods. We prospectively followed all incident CTD and PSV cases included in the Norwegian CTD and vasculitis registry (NOSVAR) between 1999 and 2015. Fifteen controls for each patient matched for sex and age were randomly drawn from the Norwegian National Population Registry. Causes of death were obtained from the National Cause of Death Register, death certificates and hospital charts.

Results. The cohort included 2140 patients (1534 with CTD, 606 with PSV). During a mean follow-up time of 9 years, 279 of the patients (13%) died, compared with 2864 of 32 086 (9%) controls ($P < 0.001$). Ten years after diagnosis, the lowest survival was 60% in dcSSc, 73% in anti-synthetase syndrome (ASS) and 75% in lcSSc. In the CTD group, the highest SMRs were observed in dcSSc (SMR 5.8) and ASS (SMR 4.1). In the PSV group, Takayasu arteritis (SMR 2.5) and ANCA-associated vasculitis (SMR 1.5) had the highest SMRs. Major causes of death were cardiovascular disease (CTD 27%, PSV 28%), neoplasms (CTD 25%, PSV 27%), chronic respiratory disease (CTD 20%, PSV10%) and infections (CTD 9%, PSV 16%).

Conclusion. We observed premature deaths across the spectrum of CTDs and PSVs, with highest SMRs in dcSSc and ASS. The overall mortality was highest in the CTD group.

Key words: mortality, standard mortality rates, survival, connective tissue disease, vasculitis

- Mortality was clearly increased in patients with connective tissue diseases and primary systemic vasculitides.
- Patients with SSc and anti-synthetase syndrome had the worst outcome.
- Deaths were more often than expected caused by cardiovascular disease, chronic respiratory disease and infections.

Introduction

Systemic inflammatory rheumatic diseases, including two major groups, the systemic CTDs and the primary systemic vasculitides (PSVs), are complex clinical syndromes. They are characterized by multi-organ affection, chronic relapsing-remitting disease courses with accrual of damage, and auto-immune features, including disease-specific autoantibodies. The CTDs and the PSVs are both widely heterogeneous disease groups, with significant

[1]Department of Rheumatology and [2]Oslo Centre for Biostatistics and Epidemiology, Research Support Services, Oslo University Hospital, [3]Division of Infection Control and Environmental Health, Norwegian Institute of Public Health and [4]Institute of Clinical Medicine, University of Oslo, Oslo, Norway

Correspondence to: Øyvind Palm, Oslo University Hospital-Department of Rheumatology Rikshospitalet, Pb 4950 Nydalen, 0424 Oslo, Norway.
E-mail: opalm@ous-hf.no

differences between the individual entities regarding age-at-onset and gender distribution. For example, SLE and Takayasu arteritis (TAK) most often affect young females, while GCA occurs in patients above 50 years [1].

Many earlier studies have indicated increased all-cause mortality in most systemic inflammatory rheumatic diseases, but the relative risk of premature death appears to vary between these diseases. Direct comparisons of mortality risk across individual CTDs and PSVs are, however, largely missing [2]. There are several possible explanations for the increased all-cause mortality. The acute onset, the relapsing-remitting disease courses and a persistent chronic disease over years may lead to irreversible damage of internal organs. In addition, the immunosuppressive drugs applied for treatment predispose for fatal infections and premature development of cardiovascular diseases (CVDs) [3].

Survival and mortality rates can be regarded as reliable indicators for disease severity across the individual CTDs and PSVs [4]. The 5-year and 10-year survival rates illustrate outcome within limited time frames. Standard mortality ratios (SMRs) estimate deaths among patients compared with age- and sex-matched controls and may identify disease-related mortality.

The causes of death may reflect the disease-related end-organ damage, the burden of chronic inflammation and the side effects of medication [5]. In SLE, fatal outcomes of CVD, infections and renal diseases are frequently reported [6]; patients with SSc may decease prematurely through cardiopulmonary complications [7, 8]; in myositis, respiratory- and cancer-related deaths are overrepresented [9]; in patients with TAK, ischaemic complications may be lethal [10]; and in ANCA-associated vasculitis, renal complications or infections can cause death [11].

Comparing outcomes between the various CTDs and PSVs by mortality rates and causes of death may give further insight into the nature of each disease and highlight distinct needs for treatment and monitoring. For example for patients with SLE, a multidimensional approach to achieving reduced disease activity, minimizing CS use and controlling hypertension has shown favourable outcome [12]. Intensified efforts to improve the follow-up of the CTDs and PSVs with the poorest prognosis should be considered. However, mortality and causes of death have usually been studied within the separate diseases. The heterogeneity of the studies is large and there are widely varying results. Consequently, it is difficult to compare mortality and causes of death between the different diseases [2].

The primary aim of this study was to estimate survival and mortality compared with age- and gender-matched controls. Second, we sought to identify the most prevalent causes of death in patients with CTDs and PSVs.

Methods

Study design

We performed a prospective, observational, case-controlled study based on the Norwegian systemic CTD and vasculitis registry (NOSVAR). All patients, 18 years of age or older, who received a definite diagnosis of CTDs or PSVs between January 1999 and December 2015 were included.

The NOSVAR registry

The registry is owned by Oslo University Hospital and managed by the Department of Rheumatology. It has no commercial interests and is approved by the Norwegian authorities. The inclusion of patients is made online by authorized physicians at the Department of Rheumatology. The included patients have given written consent prior to registration. Data registered includes each patient's unique national identification number, name, diagnosis, year of diagnosis, and year of onset of symptoms. Further data registered are diagnosis-dependent. Our department is the only specialized unit for CTDs and PSVs in Oslo and is a referral center for the national Southern and Eastern Norway health region, which has 2.9 million inhabitants, and most of the included patients are residents of this region. The completeness of NOSVAR has been estimated by comparing the prevalence of included cases with the results of population-based studies in the same area. For SSc [8], myositis [9] and TAK [13], the prevalence was similar, but for SLE [14] it was lower in NOSVAR.

Patients and controls

To avoid bias by selection, the cohort of patients consisted of all incident cases, excluding those with diagnoses set prior to 1999. The included patients ($n = 2140$) were followed up until death or study end at April 2017. The follow-up time was defined as the time interval from diagnosis until the time of death or end of the study period. The patients were all resident in Norway, and 1742 (81.4%) resided in the South-East health region.

The diagnoses were based on thorough rheumatological investigations and had to be definite. The diagnoses were usually set after consultation with several specialists of rheumatology, although fulfilling of classification criteria for diagnoses were not mandatory. Cases with overlapping diagnoses were classified according to the major symptoms. Patients with disease courses not consistent with the diagnoses were excluded.

Fifteen controls matched for each patient's year of birth, sex and residence area were randomly drawn from the Norwegian National Registry, which also provided the number of deaths among patients and controls [15]. All controls were alive at the point of time, when the corresponding patients were diagnosed. The follow-up time of the controls was similar to that of the patients. The study was approved by the Regional Committee of Medical Ethics in Southern Norway (approval number 2013/1637).

The National Cause of Death Register

The National Cause of Death Register includes all deaths in Norway and is based on death certificates. The causes of death are classified by International Classification of Disease (ICD-10) codes [16].

In our study, we linked patients included in NOSVAR to the National Cause of Death Register to obtain the underlying causes of death among our patients, using the unique national personal identification number that is obligatory for Norwegian citizens and which ensured that patients were not lost to follow-up. The linkage was performed in May 2016. To access the causes of deaths through the total period of the study and confirm the registry data, we reviewed the patient's hospital charts at the end of the study. When discrepancies were present, the data from the medical charts, including results of autopsies, were chosen.

Classification of deaths

We grouped the causes of death into several main categories according to the World Health Organization (WHO) Mortality Database [17]. CVD included ischaemic heart disease, cardiomyopathy, cerebrovascular disease, pulmonary hypertension, and other. Chronic respiratory disease (CRD) included interstitial or chronic obstructive pulmonary disease, but excluded pneumonia, which was classified under infections. The category other causes of death included renal and gastrointestinal deaths, trauma, poisoning and suicide. In cases without notifications on the death certificates or in the patient charts, the causes of death were defined as unknown.

To determine deaths related to the rheumatic disease, each patient's disease history obtained from the hospital charts and NOSVAR was carefully evaluated. Deaths caused by expected disease-related complications such as pulmonary hypertension in SSc, respiratory insufficiency in antisynthetase syndrome (ASS), acute myocardial infarction in a young female with TAK and others were classified as disease-related. The places of death and number of autopsies performed were available from the National Cause of Death Register. Causes of death among the controls were not evaluated.

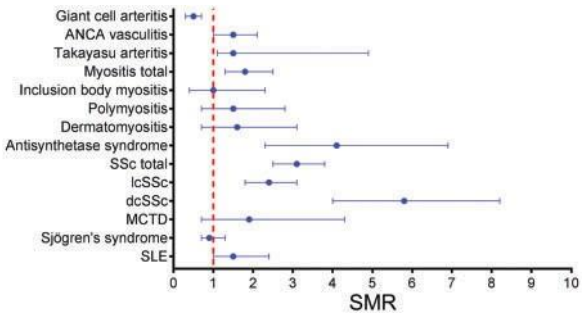
Statistical analysis

Statistical analysis was undertaken by IBM SPSS version 21 for Windows (Armonk, NY: IBM Corp.). Fig. 1 was performed with IBM SPSS version 24 and STATA software version 14. Demographical and clinical parameters were presented as means with $_{S.D.}$ or 95% CI. Pearson's chi-squared test or Fisher's exact test for contingency tables were used to compare differences between categorical independent variables. Comparisons of risk of mortality between genders were presented as odds ratios (ORs) with 95% CIs.

The controls were paired with patients within each diagnosis. Kaplan–Meier survival probabilities and curves for patients and controls were applied to determine differences in survival. For each diagnosis the difference between patients and controls was estimated by the log-rank test.

SMRs were calculated as the ratio of the number of deaths among the patients to the number of deaths among their controls. In the analyses of diagnosis-specific SMRs, the number of deaths was divided by the years under observation for each diagnosis studied. *P*-values <0.05 (two-tailed test) were considered significant.

FIG. 1 Diagnosis-specific standard mortality ratios (SMR)



The bars with spheres in the middle represent 95% CIs, and SMR. In the analyses of diagnosis-specific SMRs, the number of deaths was divided by the years under observation for each diagnosis studied.

Results

Overall mortality, mean age at death and patient location at the time of death

During the mean follow-up time of 9 years ($_{S.D.}$ 4.7, range 0.2–18), 279 of 2140 patients (13%) died, compared with 2864 of 32 086 controls (9%) ($P<0.001$) (Table 1). Overall mortality was higher in the CTD group than in the PSV group (Table 1). Men with CTDs had higher mortality (20%) than women (12%) (OR 1.4, CI 0.8–2.4), as observed in the subgroups of ASS (OR 4.1, CI 1.3–12.9) and SLE (OR 3.1, CI 1.0–9.4). In PSVs, the mortality was 14% in men and 10% in women (OR 1.4, CI 0.8–2.4). Details of age at diagnosis, mean follow-up time and mortality in the specific CTDs and PSVs are shown in Table 1.

Mean age at death in the 279 deceased patients was 70 years ($_{S.D.}$ 13), compared with 74 years ($_{S.D.}$ 11) in the 2864 deceased controls ($P<0.001$). Among the deceased patients with CTDs, the lowest mean age at death was observed in SLE, at 61 years ($_{S.D.}$19), followed by dsSSc, at 63 years ($_{S.D.}$ 11) and ASS, at 65 years ($_{S.D.}$10). In the group of PSVs, the lowest mean age at death was in TAK, at 58 years ($_{S.D.}$ 12).

Overall, 139 patients (50%) died in hospitals, 62 (22%) in nursery homes and 38 (14%) at home. Place of death was not registered for 40 patients (14%).

Survival rates and SMR

Overall, 5-and 10-year survival rates for the systemic inflammatory rheumatic diseases group were 94% and 85% (CI 15.6–16.1). Corresponding figures for the controls were 96% and 91% (CI 16.6–16.7) ($P<0.001$). Five- and 10-year survival rates differed across the individual CTDs and PSVs (Table 2). We found lower survival rates among dcSSc, ASS, lcSSc, TAK and ANCA-associated vasculitis patients compared with controls. GCA showed a higher

TABLE 1 Characteristics and demographics of patients segregated by disease

Diagnoses	Patients Total number/number of deaths, *N*/*n* (%)	Females among the patients, *N* (%)	Mean age (years) at diagnosis (S.D.)	Mean (years) follow-up time/years at risk (S.D.)	Controls Total number/ number of deaths, *N*/*n* (%)	*P*-value
Total (CTDs/PSVs)	2140/279 (13)	1627 (76)	52 (18)	9 (5)	32 086/2864 (10)	<0.001[a]
CTDs	1462/211 (14)	1201 (82)	48 (17)	10 (5)	29 161/1765 (8)	<0.001[a]
SLE	314/18 (6)	277 (88)	35 (15)	11 (5)	4710/177 (4)	0.094
SS	336/42 (13)	304 (91)	52 (14)	12 (4)	5036/641 (13)	0.917
SSc total	454/104 (23)	76 (83)	54 (14)	7 (5)	6809/552 (8)	<0.001[a]
lcSSc	329/64 (19)	285 (87)	56 (14)	8 (4)	4926/427 (9)	<0.001[a]
dcSSc	125/40 (32)	93 (74)	51 (15)	7 (5)	1875/125 (7)	<0.001[a]
Myositis total	253/41 (16)	160 (63)	53 (15)	8 (5)	3795/348 (9)	0.001[a]
PM	46/10 (22)	28 (61)	57 (13)	10 (5)	690/101 (15)	0.209
DM	74/8 (11)	51 (69)	47 (17)	8 (5)	1080/76 (7)	0.246
Anti-synthetase syndrome	96/17 (18)	66 (69)	52 (13)	7 (4)	1440/84 (6)	0.001[a]
IBM	37/6 (16)	15 (41)	61 (10)	9 (4)	600/88 (15)	0.768
MCTD	105/6 (6)	82 (78)	36 (16)	10 (5)	1575/47 (3)	0.151
PSVs	577/68 (11)	336 (58)	56 (19)	8 (4)	21 916/1765 (8)	0.002[a]
GCA	189/22 (12)	136 (77)	70 (9)	7 (4)	2835/594 (21)	0.001[a]
Takayasu arteritis	108/9 (8)	99 (79)	41 (17)	9 (4)	1635/67 (4)	0.057
ANCA vasculitis total	206/31 (15)	101 (49)	68 (8)	5 (4)	3090/324 (10)	0.049[a]
GPA	143/21 (15)	66 (46)	49 (19)	8 (4)	2145/227 (11)	0.138
MPA	30/8 (27)	22 (73)	60 (17)	6 (3)	450/40 (9)	0.007[a]
EGPA	33/2 (6)	13 (39)	54 (14)	8 (5)	495/57 (12)	0.357
PAN	13/4 (31)	6 (46)	60 (11)	9 (4)	195/24 (12)	0.098
Cogan's syndrome	11/1 (9)	4 (36)	51 (18)	10 (3)	165/22 (13)	0.384
Behçet's disease	50/1 (2)	31 (62)	36 (12)	10 (4)	742/8 (1)	0.551

[a]Significant difference in proportions of deaths between patients and controls. *N*/*n*: Total number/number of deaths. PSV: primary systemic vasculitis; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis.

TABLE 2 Survival at 5-years and 10-years, follow-up time in patients with CTDs and PSVs compared with controls

	Number at risk (*n*)	Patients			Controls			*P*-value
		Survival			Survival			
		5-years (%)	10-years (%)	Survival time Mean (95% CI)	5-years (%)	10-years (%)	Survival time, mean (95% CI)	
CTDs								
SLE	314	98	95	17.4 (17.1–17.8)	99	97	17.7 (17.6–17.8)	0.071
SS	336	97	89	16.7 (16.2–17.1)	96	90	16.6 (16.5–16.7)	0.837
SSc total	454	87	71	14.0 (13.4–14.7)	96	91	17.0 (16.5–16.8)	<0.001[a]
lcSSc	329	89	75	14.7 (13.9–15.4)	95	90	16, 6 (16.4–16.7)	<0.001[a]
dcSSc	125	79	60	12.4 (10.9–13.8)	97	92	16.9 (16.4–16.9)	<0.001[a]
Myositis total	253	91	79	15.2 (14.4–16.0)	96	90	16.4 (16.2–16.6)	<0.001[a]
DM	74	91	84	15.4 (14.2–16.6)	96	93	15.9 (15.7–16.2)	0.214
PM	46	93	75	15.1 (13.5–16.8)	96	87	16.1 (15.7–16.5)	0.202
IBM	37	96	89	15.3 (12.5–15.5)	93	86	15.3 (14.7–15.9)	0.884
Anti-synthetase syndrome	96	86	73	14.8 (13.3–16.2)	97	92	17.0 (16.6–17.2)	<0.001[a]
MCTD	105	99	93	17.3 (16.7–18.0)	99	97	17.7 (17.6–18.0)	0.118
PSVs								
Takayasu arteritis	108	96	86	16.8 (15.9–17.7)	98	96	17.5 (17.3–17.7)	0.046[a]
ANCA vasculitis	206	91	80	14.7 (13.9–15.5)	95	87	15.4 (15.2–15.6)	0.030[a]
PAN	13	—	77	12.1 (9.4–14.7)	97	87	14.7 (14.1–15.2)	0.042[a]
GCA	189	97	81	15.2 (14.0–16.4)	87	73	13.7 (13.3–14.0)	0.002[a]

The *P*-values represent difference in survival time between patients and controls. [a]Significant difference in survival time between patients and controls. PSVs: primary vasculitis syndromes.

survival rate compared with controls (Table 2). Ten years after diagnosis, the lowest survival rates among CTDs were estimated to be 60% in dcSSc, 73% in ASS and 75% in lcSSc.

Mortality expressed by SMR was highest in patients with dcSSc and in patients with ASS, with 5.8 (CI 4.0–8.2) and 4.1 (CI 2.3–6.9) times increased risk of death, respectively, followed in descending order by pa- tients with lcSSc, TAK, MCTD, DM, PM, SLE and ANCA-associated vasculitis (Table 3). Patients with GCA had the lowest SMR (Fig. 1).

Causes of death among patients

We based the causes of death on death certificates in 221 (79%), hospital records in 19 (7%) and autopsy in 30 (11%) of the deceased patients. The causes of death were not assessable in 9 patients (3%). Reasons for the missing data were delay in the Causes of Death Registry or lack of recorded data in the hospital charts. Death was deemed related to the rheumatic disease in 79 (28%), unrelated in 176 (63%) and unclassified in 25 (9%) cases. In patients with CTDs, overall, 33% suffered disease-related deaths, in descending order: dermatomyositis 57%, dcSSc 55%, ASS 53%, lcSSc 44%, SLE 21%, PM 10%, SS 2%, inclusion body myositis 1%, MCTD 0%. In PSVs, overall, 16% died due to the disease, with the following distribution: Polyarteritis nodosa 50%, TAK 33%, granulomatosis with polyangiitis 10%, GCA 9%, In microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis and Behçet's disease, no disease-related deaths were registered. The causes of death are listed in Table 4.

TABLE 3 Observed number of deaths among patients and controls

Diagnoses	Observed number of deaths among patients (*n*)	Number of deaths among controls (*n*)	SMR (95% CI)
SLE	18	177	1.5 (1.0–2.4)
SS	42	641	1.1 (1.0–1.1)
SSc total	104	552	3.1 (2.5–3.8)
lcSSc	62	419	2.4 (1.8–3.1)
dcSSc	39	126	5.8 (4.0–8.2)
Myositis total	41	348	1.8 (1.3–2.5)
DM	8	76	1.6 (0.7–3.1)
PM	10	101	1.5 (0.7–2.8)
IBM	6	88	[illegible]
Anti-synthetase syndrome	17	84	4.1 (2.3–6.9)
MCTD	6	47	1.9 (0.7–4.3)
Takayasu arteritis	9	54	2.5 (1.1–4.9)
ANCA vasculitis	31	324	1.5 (1.0–2.1)
GCA	22	595	0.5 (0.3–0.7)

In the analyses of SMR, the number of deaths was divided by the years of observation. SMR: standard mortality ratios.

Discussion

We report survival, mortality and causes of death in patients with CTDs and PSVs, recruited by similar methods across the diagnoses and followed prospectively for up to 18 years. Mortality was higher in CTDs, especially among males, compared with PSVs and varied largely within the subgroups. Fifty percent of our patients died in hospitals, which is higher than expected (30% in the general population) [16].

Deceased patients reached a mean age of 70 years, compared with 74 years among the controls, indicating that the diseases shortened the patient's life by years. Our data do, however, not represent life expectancy, because the total cohort was not followed until death. The leading causes of death were CVD, neoplasm, CRD and infections, accounting for 79% of all deaths. These causes of death were more prevalent than in similar age and gender groups in the general Norwegian population [17]. Overall, 28% of the deaths were related to the rheumatic disease.

In patients with SSc, the mean age at death and the 5- and 10-year survival rates were clearly lower compared with their controls. Moreover, the SMR indicated a more than 3-fold increase in mortality. The subgroup of patients with dcSSc had the poorest outcome, with the highest SMR (5.8) of the diseases investigated. Our results confirm the high mortality in patients with SSc found in previous surveys [8, 18, 19]. In a population-based study from our area, the 5- and 10-year survival rates (95% and 86%, respectively) were moderately higher than in our study, and the SMR (overall 2.0, dcSSc 5.3) was slightly lower [8]. This may indicate that our study has some selection of cases with poor prognoses. In a Swedish study, the 5- and 10-year survival rates were 86% and 69%, and the SMR 4.6; these results are close to ours [18]. In Italy, a 10-year survival rate of 69% was also similar to ours [19]. In these studies of SSc, including ours, dcSSc had the poorest prognosis. The leading cause of death in SSc was CVD (37%), and this was the highest rate among the CTDs, clearly higher than in the corresponding general population (11 and 22% for females and males, respectively) [17]. It was similarly distributed in dcSSc and lcSSc. The explanation for most of the premature CVD deaths in SSc is possibly related to pulmonary hypertension [8] or primary heart disease with myocardial damage, fibrosis of the conduction system and pericardium [20]. To improve survival, regular screening with annual Doppler echocardiography to detect early signs of cardiac manifestations, early intervention and optimal medical treatment should be practised [21].

ASS represented the most serious form of myositis, characterized by low mean age among the deceased and low 5- and 10-year survival rates. After dcSSc, ASS had the highest SMR (4.1) of all the investigated diseases, and the mortality was highest in men. Previous mortality data for ASS are not available from our region, but in Spain the 5-year survival rate was 87.7%, the 10-year survival rate was 75.4%, and the SMR was 4.03 [22]—these figures are close to our results. In a study

TABLE 4 Causes of death of the 279 deceased patients

	CVD	CRD	Infections	Neoplasms	Other	Unknown	Missing	Total number of deaths
Total, *n* (%)	78 (28)	39 (14)	42 (15)	70 (25)	27 (10)	14 (5)	9 (3)	279
CTDs, *n* (%)	58 (27)	34 (16)	28 (13)	51 (24)	22 (10)	12 (6)	6 (3)	211
SLE, *n* (%)	5 (28)	1 (6)	4 (22)	4 (22)		4 (22)		18
SS, *n* (%)	10 (23)	4 (10)	8 (19)	11 (26)	5 (12)	2 (5)	2 (5)	42
SSc total, *n* (%)	38 (37)	8 (7)	14 (13)	23 (22)	14 (13)	3 (5)	4 (4)	104
lcSSc, *n* (%)	25 (39)	6 (17)	9 (6)	13 (20)	7 (11)	1 (2)	3 (5)	64
dcSSc, *n* (%)	13 (33)	2 (5)	5 (13)	10 (25)	7 (18)	2 (10)	1 (3)	40
Myositis total, *n* (%)	3 (10)	11 (29)	11 (15)	12 (29)	2 (5)	2 (5)		41
PM, *n* (%)	2 (20)	1 (10)	5 (50)	1 (10)		1 (10)		10
DM, *n* (%)	1 (13)		3 (38)	4 (50)				8
Anti-synthetase syndrome, *n* (%)		9 (53)	1 (6)	6 (35)	1 (6)			17
IBM, *n*		1	2	1	1	1		6
MCTD, *n*	1	1	1	1	1	1		6
PSVs, *n* (%)	21 (31)	5 (7)	14 (21)	19 (26)	5 (7)	2 (3)	3 (9)	68
GCA, *n* (%)	9 (41)	3 (14)	1 (5)	5 (28)	2 (9)		2 (14)	22
Takayasu arteritis, *n* (%)	5 (56)		1 (11)	3 (33)				9
ANCA vasculitis total, *n* (%)	7 (19)	2 (16)	9 (29)	10 (32)		2 (3)	1 (6)	31
GPA, *n* (%)	5 (24)	1 (5)	6 (29)	6 (29)		2 (5)	1 (5)	21
MPA, *n* (%)	2 (25)	1 (13)	2 (25)	3 (38)				8
EGPA, *n*			1	1				2
PAN, *n*			2		2			4
Cogan's syndrome, *n*					1			1
Behçet's disease, *n*				1				1

CVD: cardiovascular disease; CRD: chronic respiratory disease; PSVs: primary systemic vasculitides; TAK: Takayasu arteritis; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis.

from the USA, the 10-year survival rate of 68% was lower, and, as in our study, men had the poorest prognosis [23]. The main cause of death in our patients with ASS was CRD (35%). In comparison, CRD accounts for only 3.8 and 5.4% (males and females, respectively) of the deaths in the corresponding general population [17]. This underlines the seriousness of the pulmonary involvement in ASS [24]. In ASS, observation of pulmonary symptoms and the detection of typical serological antibodies are essential for early recognition and good management [24]. Patients with pulmonary involvement should, as early as possible, be identified, because the muscular component may be mild.

In PM and DM, deaths also occurred prematurely, and we found increased SMRs, but the outcome was better than in ASS. Although there were small numbers in DM, four out of eight deaths were caused by neoplasms, which seem to confirm the high risk of malignancy [9].

Only 6% of our patients with SLE died during follow-up, but their mean age at death was quite low (61 years). This may indicate early mortality in a few cases and young age at disease onset. The outcome was overall better than in a previous population-based study from Oslo [6]. It may reflect the fact that several severe cases of SLE have not been included in NOSVAR, probably because those with specific organ involvement, such as nephritis with end-stage renal disease [25], are followed-up by nephrologists or other specialists, rather than rheumatologists.

Moreover, improved management of the disease over recent years has, in general, contributed to better prognosis [26]. The causes of death seemed to confirm a high prevalence of lethal infections in SLE [27].

In MCTD, our data indicated slightly increased mortality, but due to the small number of cases, the results should be interpreted with caution. Comparable studies using control groups from the general population are, however, lacking [28].

For primary SS (pSS), the outcome resembled that for the controls, and the causes of death were distributed as in the general population [17], which is in accordance with previous studies [29].

Among patients with PSVs, we found deaths at the youngest age in TAK (mean 58 years). Their 5- and 10-year survival rates and SMRs also indicated premature mortality. Mortality in TAK has been evaluated in a few previous studies. One obstacle to comparison is the different distribution of the manifestations, depending on the patients' ethnic background [13]. In a French study, 5% died within a median of 6.1 years since diagnosis [30], which is comparable with our results. A 10-year survival rate of 97% in the USA was better, but the SMR of 3.0 was higher than in our study [31]. These varying results may reflect different study designs, dissimilar ethnic background of the populations, and the small number of patients included in the studies. We found that CVD was the cause of death in as many as 51% of our patients with

TAK, which is much higher than expected, taking age into consideration [17]. We are not aware of comparable studies from Europe, but the results are comparable with those reported from Korea and China [32, 33]. Reasons for premature deaths by CVD in TAK are probably the typical large arterial vessel involvement, with development of stenosis, occlusions and aneurisms and risk of early acute heart infarction or stroke [13]. Moreover, premature development of atherosclerosis has been reported [34]. In TAK, the diagnostic delay should be further reduced and treatment, which may include MTX and TNF inhibitors, should be started before arterial stenosis and occlusions have developed [35].

The results for TAK differ from those for GCA, which involves large arteries, but starts at an older age. Among our patients with GCA, disease-related thoracic aneurism ruptures were lethal in two cases (data not shown). The low SMR found indicates an overall mortality lower than the controls. It is unlikely that GCA improved life expectancy; however, the diagnosis may have led to further clinical investigations and closer follow-up, leading to better management of coexisting hypertension, diabetes and atherosclerosis, improving survival in some cases [36], similarly to findings in PMR [37].

In ANCA-associated vasculitis, we found increased mortality, with the highest death rates in MPA, although not disease-related in most cases. Our patients had an overall better prognosis compared with the patients in a previous meta-analysis, which showed an SMR of 2.71 among 3338 patients [38]. The meta-analysis included, however, older cohorts, with patients enrolled during the 1980s. By analyzing the data gained between 2000 and 2005, they found an SMR of 1.92, which is close to our result. The reason for declining mortality over time in ANCA-associated vasculitis is probably due to more treatment options and better management [11]. The causes of death among our patients with ANCA-associated vasculitis were almost identical to those in the corresponding general population [17].

Our study has limitations. By investigating many diseases at the same time, we added perspective, but precision and detailed information on each diagnosis may have suffered. It is a single-centre study with a limited number of patients included, making statistical estimations less accurate, especially in subgroups of the rarest diagnoses. Results with wide CIs should therefore be interpreted carefully. Our study is not population-based. Thus, selection of severe cases with reduced survival may have occurred (e.g. in SSc). Moreover, our special interest in some diseases, including MCTD, SSc and TAK, may have led to a higher number of referrals to our department and higher inclusions of these diseases. On the other hand, diseases with specific, severe organ manifestation (e.g. nephritis in SLE) may have missed inclusion. We based the diagnoses on routine diagnostic and follow-up data and did not use classification criteria. Principally, this may result in inhomogeneous cohorts. However, classification criteria change with time, and over the two decades of this study, multiple criteria within single diseases could have been applied, with the risk of erroneously excluding cases [39]. Unfortunately, the results of laboratory data, patient's medications, smoking habits and comorbidity were not accessible for analysis in our study.

Advantages of the study are the consecutively enrolment of patients and follow-up in a registry, which may reduce selection of severe cases and exclude cases not consistent with the diagnoses. The inclusion by similar methods across all diagnoses of CTDs and PSVs should reduce the risk of selection within the specific diseases.

In conclusion, mortality was clearly increased in patients with CTDs and PSVs compared with the controls. Patients with SSc and ASS had the worst outcome. Deaths in CTDs and PSVs were more often caused by CVD, CRD and infections than would be expected in the general population. Our results underline the importance of being alert to early symptoms of serious manifestations in CTDs and PVSs and starting treatment as early as possible. Due to the complexity of the diseases, a multidimensional approach to reducing disease activity, minimizing CS use and controlling organ manifestations over time may still be required in order to achieve the most favourable outcomes possible.

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