Title: Acute coronary syndrome in idiopathic inflammatory myopathies: a population-based study

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Abstract

Objective

Evidence suggest an increased risk of cardiovascular diseases including acute coronary syndrome (ACS) in idiopathic inflammatory myopathies (IIM). The aim of this study was to investigate the risk of ACS in an incident IIM cohort compared to the general Swedish population.

Methods

A cohort of 655 incident IIM individuals and 6813 general population comparators were identified from national registries. IIM subjects were diagnosed from 2002 to 2011. Follow-up started at IIM diagnosis and corresponding date in the general population. ACS, cardiovascular comorbidities and cardiovascular risk factors were defined using ICD codes. Incidence rates including 95% confidence intervals (CI) were calculated. Cox proportional hazards models were used to compare the risk of ACS in IIM patients and the general population. The competing risk of death was accounted for using competing risk regression models.

Results

The incidence rate of ACS in IIM was higher than in the general population particularly within the first year of diagnosis and in older individuals. The overall ACS incidence rate (95% CI) in IIM was 15.6 (11.7-20.4) per 1000 person-years with a hazard ratio (95% CI) of 2.4 (1.8-3.2) compared with the general population. When accounting for the competing

risk of death, the risk of ACS in IIM remained increased with a cumulative incidence of 7% at 5 years compared to 3.3% in the general population.

Conclusion

IIM individuals are at higher risk of ACS particularly within the first year after diagnosis.

Introduction

Idiopathic inflammatory myopathies (IIM) are a group of chronic autoimmune multisystemic diseases often characterized by muscle inflammation and muscle weakness. The major IIM subsets are dermatomyositis (DM), polymyositis (PM), inclusion body myositis (IBM) and immune-mediated necrotizing myopathies (1). Morbidity and mortality are still higher in IIM than in the general population despite advances in the field and introduction of novel therapies (2, 3). Evidence suggest an increased risk of cardiovascular disease, such as arrhythmias, congestive heart failure and acute coronary syndrome (ACS), in IIM individuals (4-9). The burden of cardiovascular diseases is of major concern in several rheumatologic conditions, notably rheumatoid arthritis and systemic lupus erythematosus (10, 11). In IIM, the higher prevalence of traditional cardiovascular risk factors coupled with a chronic inflammatory state and possibly vasculitis could account for an added ACS risk (12-15). A majority of published studies to date have investigated the risk of ACS in prevalent IIM cohorts that lacked comparators and/or used combined cardiovascular endpoints (4-7). A recent Canadian population-based study reported a 3- to 4-fold increased risk of myocardial infarction in DM and PM individuals after adjustment for medication use (9). However, unstable angina was not considered, stratification for gender or age was not included and the impact of time on myocardial infarction incidence was assessed only up to five year after diagnosis. The aim of the present study was to investigate the risk of ACS in a large incident IIM cohort compared to the general Swedish population.

Materials and methods

Study design

This population-based cohort study includes incident IIM patients (exposed) and matched comparators from the general population (unexposed).

Setting

The Swedish healthcare coverage is universal thus all residents have access to publicly funded inpatient and outpatient healthcare. IIM individuals are usually diagnosed and followed by internists, rheumatologists, dermatologists or neurologists practicing in hospital-based settings. The unique personal identification number given to all residents enables data retrieval from national administrative databases and clinical registries, with linkage of demographic, morbidity and mortality data.

Study population

The Swedish National Patient Register (NPR; 1964-2012) indexes data on hospitalizations from 1987 and outpatient visits from 2001. Clinicians are allowed to allocate a main diagnosis and up to 10 contributory diagnoses for each hospitalization. The NPR coverage is almost universal for hospitalizations and most IIM subjects (95%) are followed by hospital-based specialists resulting in a high coverage of outpatient visits in that population. The adult ($\geq$18 years) incident IIM cohort was identified from the NPR using the International Classification of Diseases 10th revision (ICD-10) codes for IIM (juvenile DM M33.0, DM M33.1, PM M33.2, 33.9 and IBM G72.4). The IIM case definition used in this study was used in previous publications and showed a positive predictive value and a sensitivity of >85% for all ICD codes except IBM (16, 17). Based on this

algorithm, to be included in our cohort an individual was required to have 1) ≧ two visits indexed with an IIM diagnosis by a specialist (dermatologist, internist, neurologist or rheumatologist), 2) an initial visit between 2002 and 2011 and 3) a follow-up visit within one year listing an IIM code. We had access to data from 2001 to 2012, allowing us to exclude prevalent IIM cases that had received an IIM code in the year prior to the study period (2001) while following-up on cases included in 2011. This approach accurately identifies DM individuals, but PM and IBM are considered together under "other IIM" due to coding overlap. Each IIM subject was matched up to 1:10 on age, gender, and place of residence with randomly selected individuals from the general population identified through the Swedish Population Register. Comparators were required to be alive and residing in Sweden at the index date of their matched IIM subject. This study got the approval from the Regional Ethical Committee of Stockholm (2017/2000-31).

Definition of outcome

The primary outcome of this study was the occurrence of the first-ever ACS during follow-up period. ICD 10 codes used to identify ACS from hospitalization records as primary discharge diagnosis and cause of death register were I20.0 for unstable angina and I21 (all sub-categories) for acute myocardial infarction including non-ST-elevation (NSTEMI) and ST-elevation myocardial infarction (STEMI). ACS identification using ICD codes has been shown to be valid and the definition of ACS used in this study previously showed a positive predictive value of 95% (18, 19). All individuals with a history of ACS at baseline were excluded.

Covariates

Gender and date of birth were extracted from the *Swedish Population Register.* Presence of cardiovascular comorbidities and risk factors at baseline were identified using in- and outpatient visits from the *NPR* indicating either stroke (I61, I63), atrial fibrillation (I48), stable angina (I20.9), heart failure (I42, I50), diabetes (E10, E11) and/or hypertension (I10, I11, I12, I13, I15) in the year preceding the index date (20-24). In addition, the *Prescribed Drug Register (PDR),* including data on prescriptions filled across Sweden since 2006, was used to identify individuals treated for cardiovascular diseases or risk factors, and those exposed to medications that increase cardiovascular risk in the 6 months preceding the index date. The *PDR* was also used to determine immunosuppressive therapies received +/- 2 months from index date (details in Supplementary Table 2). Educational level was retrieved from the *Longitudinal Integration Database for Health Insurance and Labour Market Studies* and used as a measure of socio-economic status (25).

Index date and follow-up

The date of the second visit recorded was considered the index date in the IIM cohort. The follow-up started at this point and ended at first ACS, first emigration, death or December 31st, 2013, whichever occurred first.

Statistical analyses

Descriptive statistics were used to summarize characteristics of IIM individuals and general population comparators at baseline and at first ACS. Crude incidence rates per

1000 person-years were calculated by dividing the number of ACS events by the follow-up period and were stratified by gender, age at diagnosis and IIM subsets. Confidence intervals (CI) were calculated assuming a Poisson distribution using the exact method (26). The association between IIM and ACS was estimated using Cox proportional hazards models and expressed as hazard ratios (HR). This approach considers that ACS and death are independent, while they are in fact competing. To account for the competing risk of death, the sub-distribution HR (sd-HR) and cumulative incidences of ACS at 1, 5 and 10 years for both group were estimated using Fine and Gray competing risk regression models (27). All models were adjusted for age at index date as a continuous variable, birth year, year of IIM diagnosis, gender, and residential area. In order to determine if the risk of ACS was higher at diagnosis, HR of ACS stratified by time since index date (<1, 1-5 years, 5-12 years) were obtained using time-dependent covariates. A p-value of <0.05 was considered statistically significant. All analyses were performed using SAS software package version 9.4 (SAS Institute, Cary, NC), R version 3.3.3 and STATA IC 11.2.

Results

We included 655 incident IIM individuals and 6813 age and gender-matched general population comparators. Sixty-one IIM subjects and 287 comparators were excluded given prior ACS. Baseline characteristics of both groups are presented in Table 1. Fifty-six percent were women and a third of the patients were DM. The prevalence of atrial fibrillation and hypertension was slightly lower in the general population comparators than in patients with IIM. The subgroup of individuals with available medication data revealed

a higher proportion of IIM subjects exposed to cardiovascular drugs than the comparators (Table 2). The use of statins or fibrates was however lower in the IIM individuals, but a higher proportion of them were exposed to acetylsalicylic acid (ASA). As expected, a large proportion of the IIM group received immunosuppressive drugs around the index date. Fifty-three ACS occurred in the IIM group compared to 313 in the general population with a similar age and gender distribution (Table 3). IIM subjects experienced their first ACS sooner in the follow-up period than the comparators (median (IQR) years 2.4 (1.0-4.6) vs 3.5 (1.8-6.0)).

Incidence rate of ACS

The crude incidence rate for ACS (95% CI) in the IIM cohort was 15.6 (11.7-20.4) per 1000 person-years, and 7.6 (6.7-8.4) per 1000 person-years in the general population (Table 4). The age and gender-adjusted rate difference (95% CI) was 5.7 (2.2-9.3). The incidence rates of NSTEMI and STEMI were higher in the IIM group. In the general population, ACS incidence rates were higher in males, and in older individuals. In the IIM group, older subjects and those with inflammatory myopathies other than DM had the highest incidence rates. In contrast with the general population, incidence rates in women and men were similar in the exposed group.

Association between IIM and ACS

The overall age, gender and residential area-adjusted HR (95% CI) comparing the IIM cohort and the general population was 2.4 (1.8-3.2). The increased relative risk was highest in women, in the 68-90 years-old subgroup and in the “other IIM” group compared

with the general population (Table 4). The relative risk of ACS in DM individuals was similar to the general population. When stratified by time since diagnosis, the HR (95% CI) for ACS was highest within a year from IIM diagnosis (3.6 (1.9-6.7)), decreasing thereafter (Table 5). When the association of IIM and ACS was estimated by a competing risk model, considering death the competing event, the overall sd-HR (95% CI) was 1.9 (1.4-2.5). The cumulative incidence (95% CI) of ACS estimated using Fine and Gray competing risk models adjusted for age, sex and place of residence at one, five and ten years was 2 (1.2-3.4), 7.0 (5.2-9.5) and 12.0 (8.9-16) percent in the IIM cohort, and 0.62 (0.46-0.83), 3.3 (2.9-3.8) and 6.9 (6.1-7.8) percent in the general population.

Discussion

In this large population-based nationwide study looking at ACS risk in IIM, we found an increased incidence and relative risk of ACS in IIM individuals compared with the general population. In our IIM cohort, the ACS incidence rate was 15.6 (11.7-20.4) per 1000 person-years and the HR (95% CI) 2.4 (1.8-3.2) for IIM compared to general population comparators. As IIM individuals have a significantly higher mortality rate compared with the general population, it is important to take death into account when interpreting their risk of experiencing an ACS (3). When accounting for the competing risk of death, the sd-HR (95% CI) of ACS in our IIM cohort remained increased at 1.9 (1.4-2.5) with a cumulative incidence of ACS of 7% at 5 years compared to 3.3% in the general population. In a Canadian cohort study, a similar ACS incidence rate was found in PM/DM individuals (13.8/1000 p-y) with an ACS relative risk (95% CI) of 1.95 (1.35-2.72) compared with the general population (7). The risk of ACS in this study was highest in the

first year after diagnosis and decreased in the subsequent years, similar to our results. We can hypothesize that some factors in the period following diagnosis such as introduction of immunosuppression or higher IIM disease activity might influence ACS risk. Further studies are however necessary to elucidate why this period is critical in the development of ACS in IIM. In our study, after IIM subset stratification, a 2-fold ACS risk increase was only seen in IIM individuals not affected by DM. These results are differing from a recent large population-based study reporting HR (95% CI) for myocardial infarction in PM of 3.89 (2.28-6.65) and in DM of 2.92 (1.48-5.78) (9). The discrepancy between our results could not be accounted simply by differences in case and outcome definitions but could be due to the small number of events (n=8) recorded in this subgroup.

In this study, a higher proportion of IIM individuals were receiving medication to treat cardiovascular diseases at baseline compared to the general population. However, IIM individuals were less exposed to statins and/or fibrates. Myalgias and mild elevation of serum creatinine kinase are frequent side effects of statins (28). In certain IIM individuals at the early stage of disease, statins might be discontinued for suspicion of statin-induced muscle toxicity and might not be re-introduced afterwards. This might affect the ACS risk in the IIM population. Even if medication data was available for only 60% of our cases/controls and could not be use in our model, we consider this sample representative and comparable to the rest of the cohort.

When comparing our IIM cohort with the general population, a 3-fold increase in ACS relative risk was observed in elderly and female IIM individuals. To our knowledge, this is the first study to report a gender difference in the risk of developing ACS in IIM individuals when compared with the general population. Even if the crude incidences were similar between males and females, the relative risk of ACS when compared with the general population was clearly higher in female. In a Swedish population-based RA study, such a gender difference in ACS risk was not found (29). Despite being exposed to a similar inflammatory state, RA female patients in the aforementioned study had a lower incidence rate of ACS compared to male. In our study, both genders have similar incidence rates, suggesting that the mechanisms underlying ACS in the IIM population could differ from other rheumatologic diseases. This notion should also be taken into consideration when clinicians consider cardiac risk stratification in that population. Histopathologic data revealed that 40% of IIM individuals have myocarditis on autopsy, a condition that might be clinically difficult to differentiate from an ACS without advanced imaging such as cardiac magnetic resonance (30). In addition, a recent cross-sectional study of 47 PM/DM subjects described myocardial inflammation in 60% of the patients (31). Even if those individuals were not all considered to have myocarditis, myocardial inflammation may surely influence ACS diagnosis in that population. The distinction between those two conditions is however important, since myocarditis requires aggressive immunosuppression.

This is one of the largest population-based study to assess ACS risk in an incident IIM cohort including IBM patients. The inclusion of this particular subset might underestimate

the ACS incidence rate in the "other IIM" subgroup. Evidence are suggesting that cardiac abnormalities are not increased in IBM compared to elderly individuals (32). To our knowledge, cardiac involvement in IBM at disease onset has never been assessed probably due to the usually long delay before diagnosis. This underlines a limitation of our study, where coding overlap limited our ability to divide our IIM cases in the different classic IIM subgroups (PM, DM, IBM). The large "other IIM" subgroup is therefore heterogeneous, and most likely contains subsets that are more at risk of ACS than others. Even if we based our case ascertainment on a robust case definition for IIM, there is still a risk of misclassification given that our IIM cases were not confirmed by imaging or histopathology. Additionally, diagnosis is often delayed in IIM, with patients developing symptoms several years before diagnosis. Our approach is excluding those subjects that might have had their ACS in their "latency period", which would underestimate the ACS risk in our cohort. It is possible that some comorbidities such as hypertension and atrial fibrillation were detected more frequently in IIM patients as a result of a surveillance bias. Administrative data also did not allow for stratification by autoantibody status. Phenotypes based on autoantibody profiles are characterized by different extramuscular involvement and might be associated with different ACS risk. Smoking and obesity are known risk factors for CVD and are important confounders in this type of study, but were not available for inclusion in our analyses.

Conclusion

This large population-based study clearly demonstrates an increased risk of ACS in IIM particularly in the year following diagnosis and in older individuals. Future collaborative

studies are needed to understand the mechanisms underlying ACS in IIM, taking in consideration IIM subsets and autoantibody profiles.

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Table legends

Table 1. Baseline characteristics of incident IIM cases and matched general population comparators

Numbers are n (%), unless specified.

IQR, interquartile range; SD, standard deviation; IIM, idiopathic inflammatory myopathy.

Table 2. Baseline characteristics of incident IIM cases and matched general population comparators with available medication records

Numbers are n, (%), unless specified.

IQR, interquartile range; SD standard deviation; IIM idiopathic inflammatory myopathy; NSAIDs, nonsteroidal anti-inflammatory drugs; COX, cyclooxygenase.

*Including calcineurin inhibitors, methotrexate, azathioprine, mycophenolate mofetil, and hydroxychloroquine.

Table 3. Characteristics of study population at first acute coronary syndrome

Numbers are n (%), unless specified. NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; IQR, interquartile range; SD, standard deviation.

Table 4. Number of ACS, follow-up, incidence rates, rate differences and hazard ratios (HR) for ACS overall and stratified by gender, age group and IIM subset for all the IIM individuals and matched general population comparators included in the study

Follow-up in person-years. Incidence rate per 1000 person-years, CI estimated using a Poisson distribution. Hazard ratios (HR) estimated by Cox models adjusted for age, sex, county of residence at index year. Rate differences (RD) estimated using a Poisson model adjusted for age (tertiles) and sex.

IIM, idiopathic inflammatory myopathy; ACS, acute coronary syndrome; UA, unstable angina; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; n, number of ACS; F/U, follow-up; DM, dermatomyositis; IIM, idiopathic inflammatory myopathy.

Table 5. Number of ACS, follow-up and hazard ratios (HR) for ACS stratified by time since diagnosis for IIM individuals and general population comparators

n=number of ACS. Follow-up in person-years. Hazard ratios (HR) estimated by Cox models adjusted for age, sex and county of residence at index year. IIM, idiopathic inflammatory myopathy

Supplementary Table 1. ICD codes used to identify idiopathic inflammatory myopathies, acute coronary syndrome and cardiovascular comorbidities or risk factors

*Includes ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI)

DM, dermatomyositis; PM, polymyositis; IBM, inclusion body myositis.

Supplementary Table 2. ATC codes used to identify medications at baseline

NSAIDs, nonsteroidal anti-inflammatory drugs; COX, cyclooxygenase; IIM, idiopathic inflammatory myopathies.

	IIM individuals n=655	General population n=6813
Follow-up, median (IQR)	4.5 (2.5-8.0)	6.0 (3.4-8.9)
Women	367 (56)	3821 (56)
Age, mean (SD), years	60 (15)	61 (15)
Age group		
<56	223 (34)	2242 (33)
56 - < 68	215 (33)	2255 (33)
68 - ≤ 90	217 (33)	2316 (34)
Educational level		
<10 years	205 (31)	2172 (32)
10 – 12 years	269 (41)	2741 (40)
>12 years	171 (26)	1795 (26)
Missing	10 (2)	105 (2)
Diagnosis		
Dermatomyositis	218 (33)	
Other IIM	437 (67)	
Cardiac comorbidities		
Stroke	15 (2)	166 (2)
Atrial fibrillation	40 (6)	256 (4)
Stable angina	21 (3)	167 (2)
Heart failure	20 (3)	103 (2)
Diabetes	28 (4)	253 (4)
Hypertension	88 (13)	591 (9)

Table 1. Baseline characteristics of incident IIM cases and matched general population comparators

Numbers are n (%), unless specified.

IQR, interquartile range; SD, standard deviation; IIM, idiopathic inflammatory myopathy.

	IIM individuals n=397	General population n=4166
Follow-up, median (IQR)	3.5 (2.3-5.5)	4.1 (2.8-6.0)
Women	216 (54)	2273 (55)
Age, mean (SD), years	61 (15)	62 (15)
Diagnosis		
Dermatomyositis	144 (36)	
Other IIM	253 (64)	
Cardiac comorbidities		
Stroke	11 (3)	116 (3)
Atrial fibrillation	27 (7)	193 (5)
Angina	15 (4)	119 (3)
Heart failure	14 (4)	85 (2)
Diabetes	19 (5)	175 (4)
Hypertension	76 (19)	470 (11)
Medications		
Cardiovascular drugs	231 (58)	1589 (38)
Acetylsalicylic acid	79 (20)	514 (12)
Anti-diabetics	43 (11)	261 (6)
Statins, fibrates	46 (12)	664 (16)
NSAIDs, COX2 inhibitors	101 (25)	510 (12)
Hormonotherapy	5 (1)	44 (1)
Corticosteroids	289 (73)	148 (4)
Other immunosuppressors*	178 (45)	42 (1)

Table 2. Baseline characteristics of incident IIM cases and matched general population comparators with available medication records

Numbers are n, (%), unless specified.

IQR, interquartile range; SD standard deviation; IIM idiopathic inflammatory myopathy; NSAIDs, nonsteroidal anti-inflammatory drugs; COX, cyclooxygenase.

*Including calcineurin inhibitors, methotrexate, azathioprine, mycophenolate mofetil, and hydroxychloroquine.

	IIM individuals	General population
Number of events	53	313
Unstable angina	2 (4)	28 (9)
NSTEMI	17 (32)	103 (33)
STEMI	34 (64)	182 (58)
Women	30 (57)	136 (43)
Age at event, mean (SD), years	70 (11)	70 (11)
Time to event, median (IQR) year	2.4 (1.0-4.6)	3.5 (1.8-6.0)
Cardiac comorbidities		
Stroke	1 (2)	16 (5)
Atrial fibrillation	6 (11)	19 (6)
Stable angina	4 (8)	28 (9)
Diabetes	4 (8)	30 (10)
Hypertension	10 (19)	46 (15)
Heart failure	2 (4)	10 (3)

Table 3. Characteristics of study population at first acute coronary syndrome

Numbers are n (%), unless specified. NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; IQR, interquartile range; SD, standard deviation.

	IIM individuals			General population				
	n	F/U	Rate (95% CI)	n	F/U	Rate (95% CI)	RD (95% CI)	HR (95% CI)
ACS	53	3402	15.6 (11.7-20.4)	313	41783	7.5 (6.7- 8.4)	5.7 (2.2-9.3)	2.4 (1.8-3.2)
UA	2	3402	0.6 (0.1-2.1)	28	41783	0.7 (0.4-1.0)	-0.2 (-0.5-0.1)	0.9 (0.2-3.7)
NSTEMI	17	3402	5.0 (2.9-8.0)	103	41783	2.5 (2.0-3.0)	1.8 (-0.1-3.8)	2.3 (1.4-3.9)
STEMI	34	3402	10 (6.9-14.0)	182	41783	4.4 (3.7-5.0)	4.0 (1.2-6.8)	2.8 (1.9-4.0)
Gender								
Female	30	1934	15.5 (10.5-22.1)	136	24179	5.6 (4.7- 6.7)	7.4 (2.6-12.2)	3.4 (2.3-5.0)
Male	23	1469	15.7 (9.9-23.5)	177	17604	10.1 (8.6-11.7)	3.9 (-1.4-9.2)	1.8 (1.2-2.8)
Age group								
<56	7	1424	4.9 (2.0-10.1)	33	15447	2.1 (1.5- 3.0)	2.7 (-0.9-6.3)	2.4 (1.1-5.5)
56 - <68	11	1145	9.6 (4.8-17.2)	84	13870	6.1 (4.8- 7.5)	4.0 (-1.8-9.9)	1.6 (0.8-3.0)
68 - ≤90	35	834	42 (29.2-58.4)	196	12466	15.7 (13.6-18.1)	26.5 (12.5-40.6)	2.8 (1.9-4.1)
Subset								
DM	8	1066	7.5 (3.2-14.8)	85	13498	6.3 (5.0- 7.8)	1.4 (-4.0-6.8)	1.2 (0.6-2.5)
Other IIM	45	2337	19.3 (14.0-25.8)	228	28276	8.1 (7.1- 9.2)	11.4 (5.7-17.1)	2.5 (1.8-3.4)

Table 4. Number of ACS, follow-up, incidence rates, rate differences and hazard ratios (HR) for ACS overall and stratified by gender, age group and IIM subset for all the IIM individuals and matched general population comparators included in the study

Follow-up in person-years. Incidence rate per 1000 person-years, CI estimated using a Poisson distribution. Hazard ratios (HR) estimated by Cox models adjusted for age, sex, county of residence at index year. Rate differences (RD) estimated using a Poisson model adjusted for age (tertiles) and sex.

IIM, idiopathic inflammatory myopathy; ACS, acute coronary syndrome; UA, unstable angina; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; n, number of ACS; F/U, follow-up; DM, dermatomyositis; IIM, idiopathic inflammatory myopathy.

	IIM individuals		General population		
	n	Follow-up	n	Follow-up	HR (95% CI)
Time since diagnosis					
< 1 year	13	620	42	6759	3.6 (1.9-6.7)
1 - 5 years	28	2385	158	28408	2.4 (1.6-3.7)
5 - 12 years	12	2481	113	32445	1.8 (1.0-3.3)

Table 5. Number of ACS, follow-up and hazard ratios (HR) for ACS stratified by time since diagnosis for IIM individuals and general population comparators

n=number of ACS. Follow-up in person-years. Hazard ratios (HR) estimated by Cox models adjusted for age, sex and county of residence at index year. IIM, idiopathic inflammatory myopathy