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Patients with non-Jo-1 anti-tRNA-synthetase autoantibodies have worse survival than Jo-1 positive patients

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Abstract

Objective—To compare the cumulative survival and event free survival in patients with Jo-1 versus non-Jo-1 anti-tRNA synthetase autoantibodies (anti-synAb).

Methods—Anti-synAb positive patients initially evaluated from 1985 to 2009 were included regardless of the connective tissue disease (CTD) diagnosis. Clinical data were extracted from a prospectively collected database and chart review. Survival between Jo-1 and non-Jo-1 was compared by log rank and Cox proportional hazards methods.

Results—202 patients possessed anti-synAb: 122 Jo-1 and 80 non-Jo-1 (35 PL-12; 25 PL-7; 9 EJ; 6 KS; 5 OJ). The diagnoses at first visit for Jo-1 and non-Jo-1 patients were myositis in 83% and 40.0%, overlap or undifferentiated CTD in 17% and 47.5%, and systemic sclerosis in 0% and 12.5%, respectively ($p < 0.001$). The median delay in diagnosis was 0.4 years in Jo-1 patients versus 1.0 year in non-Jo-1 patients ($p < 0.001$). The most common causes of death in the overall cohort were pulmonary fibrosis in 49% and pulmonary hypertension in 11%. The 5- and 10-year unadjusted cumulative survival was 90% and 70% for Jo-1 patients, and 75% and 47% for non-

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Contributors I certify that neither this manuscript nor one with substantially similar content under my authorship has been published or is being considered for publication elsewhere (except as indicated in an attachment). I have access to all data upon which the manuscript is based and will provide such data upon request to the editors or their assignees. I agree to allow the corresponding author to correspond with the editorial office, to review the uncorrected proof copy of the manuscript; and to make decisions regarding release of information in the manuscript. I have given final approval of the submitted manuscript for which I take public responsibility for whole content. According to the definition given by the International Committee of Medical Journal Editors (ICMJE), I and all other coauthors qualify for authorship based on making one or more of the substantial contributions to the intellectual content: conception and design, acquisition of data, and analysis and interpretation of data. Furthermore, I and all coauthors have participated in drafting of the manuscript and critical revision of the manuscript for important intellectual content. I am the corresponding author.

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Jo-1 patients ($p < 0.005$). The hazard ratio (HR) of non-Jo-1 patients compared with Jo-1 patients was 1.9 ($p = 0.01$) for cumulative and 1.9 ($p = 0.008$) for event free survival from diagnosis. Age at first diagnosis and diagnosis delay but not gender, ethnicity and CTD diagnosis influenced survival.

Conclusions—Non-Jo-1 anti-synAb positive patients have decreased survival compared with Jo-1 patients. The difference in survival may be partly attributable to a delay in diagnosis in the non-Jo-1 patients.

Anti-tRNA synthetase autoantibodies (anti-synAbs) target aminoacyl-tRNA synthetase enzymes, a family of cytoplasmic proteins that participate in protein synthesis by catalysing the attachment of amino acids to their specific tRNA. To date, there are autoantibodies to eight distinct aminoacyl-tRNA synthetases which, as a group, are the most common of the myositis specific autoantibodies and are seen in up to 35%–40% of patients with idiopathic inflammatory myopathy (IIM).¹ While anti-Jo-1 is the most commonly detected anti-synAb occurring in up to 30% of IIM patients, the other anti-synAb (non-Jo-1) are collectively found in 10%–20% of myositis patients.²³ The ‘antisynthetase syndrome’ refers to a collection of some or all of the following features: myositis, interstitial lung disease (ILD), inflammatory arthropathy, Raynaud phenomenon, fever and ‘mechanic’s hands’⁴ along with one of the anti-synAbs. Despite these unifying features, phenotypic differences exist between Jo-1 positive and non-Jo-1 anti-synAb positive patients, with the latter often demonstrating ILD in the absence of muscle involvement.^{35–12}

ILD is frequent in IIM, occurring in up to 46% of polymyositis/dermatomyositis (PM/DM) patients and 89% of individuals possessing anti-synAbs.¹³ While some literature supports the notion of ILD as a major cause of morbidity and mortality in IIM, other studies report no impact of ILD on overall survival—suggesting limited influence of anti-synAb positivity on patient outcomes.^{14–19} There is a paucity of literature comparing outcomes among patients with different anti-synAb. We report findings on a large cohort of patients with anti-synAbs evaluated at a single tertiary centre over a 24-year period with prospectively collected clinical data and complete serological testing. The aims of this study were (1) to compare the long-term outcome (lung transplant, survival) and cause of death between Jo-1 and non-Jo-1 anti-synAb positive patients and (2) to explore the reasons for these differences among patients possessing Jo-1 versus non-Jo-1 anti-synAbs.

PATIENTS AND METHODS

Patients

The University of Pittsburgh Connective Tissue Disease (CTD) Registry encompasses more than three decades of prospective data and serum collected on consecutive outpatients and inpatients with various autoimmune diseases evaluated at the University of Pittsburgh. All variables (clinical, laboratory, radiographic and pathological) as well as organ system definitions are well defined and standardised in this registry. The anti-synAb group included patients in the CTD registry who were initially seen between January 1985 and December 2009 with a serum specimen positive for an anti-synAb, regardless of the CTD diagnosis. This was further divided into a Jo-1 and non-Jo-1 group for comparison. A matching cohort

of patients positive for anti-SRP and anti-Mi-2 autoantibodies were selected from the CTD registry to serve as non-anti-synAb control groups representing phenotypically distinct subgroups of IIM. All patients with the diagnosis of myositis met the independent published criteria of Bohan and Peter.²⁰²¹ The diagnoses of systemic sclerosis (SSc), undifferentiated CTD (UCTD) and overlap syndrome were made clinically by experienced rheumatologists.

Serological data

Anti-SRP, anti-Mi-2 and anti-synAbs were detected using a combination of protein and RNA immunoprecipitation (IP) in our research labs as previously described (see online supplement 1).²²²³

Clinical data

The prospective CTD registry database, combined with a retrospective review of the electronic medical record (EMR) for missing data, was used to summarise the presenting clinical features and serological status, CTD diagnosis and organ system involvement during follow-up. Organ system definitions are as follows: (1) vascular (presence of Raynaud phenomenon, digital pitting scars, ulcers or gangrene, or abnormal nailfold capillaries), (2) cutaneous (DM rash or sclerodactyly), (3) joint based on objective joint swelling and tenderness, (4) muscle (objective proximal muscle weakness on manual muscle testing plus any one of the following: elevated serum creatine kinase, myopathic electromyogram or myositis on muscle biopsy), (5) gastrointestinal (proximal or distal oesophageal dysmotility or small/large bowel involvement of SSc), (6) pulmonary (fibrosis on chest radiograph or high-resolution CT) and (7) primary pulmonary artery hypertension (PAH) (mean PA pressure of >25 mm Hg on cardiac catheterisation or PA systolic pressure of >40 mm Hg detected on echocardiogram, in the absence of significant pulmonary and/or cardiac disease causing secondary pulmonary artery hypertension (PAH)).

Outcome data

The CTD database and/or EMR provided outcome information on lung transplant and mortality. Patients with an unknown status or indeterminate cause of death were submitted to the National Death Index (NDI) and the resultant cause of death codes, along with independent chart review by one physician (CVO), were used to determine the primary cause of death. All patients with unknown clinical status and no NDI match were submitted to the Social Security Death Index (SSDI) to determine status and date of death. Cumulative and event free survival (event was defined as lung transplant or death) of autoantibody subgroups were calculated.

Statistics

Baseline clinical characteristics of Jo-1 and non-Jo-1 patients, as well as SRP and Mi-2 positive patients were compared using t test, χ^2 test or Mann–Whitney test based on distribution. Kaplan–Meier survival curves and the log rank test were used to compare cumulative and event free survival between (1) Jo-1 versus non-Jo-1 anti-synAb positive patients, (2) autoantibody subsets within the non-Jo-1 anti-synAb cohort and (3) anti-synAb versus non-anti-synAb control patients. Cox proportional hazards ratios were calculated to

compare overall and event free survival after controlling for covariates including gender, ethnicity, age at initial and final diagnosis, and diagnosis delay.

RESULTS

Baseline clinical and serological characteristics

Of the 3880 patients (667 with definite or probable IIM) seen and entered in the CTD database from 1985 to 2009, 202 (5.2%) were anti-synAb positive. While 122 patients possessed anti-Jo-1 antibodies, 80 had non-Jo-1 anti-synAbs. Of the non-Jo-1 patients, PL-12 and PL-7 were most frequent at 17% (35/202) and 12% (25/202), respectively, while the remainder included nine EJ, six KS and five OJ positive individuals. Of the 202 patients possessing anti-synAbs, 133 were probable or definite IIM, by Bohan and Peter criteria.²⁰²¹ The anti-nuclear antibody (ANA) was positive in about 50% of both Jo-1 and non-Jo-1 patients (62/119 vs 38/80).

Demographic characteristics were similar between the Jo-1 and non-Jo-1 patients (table 1). However, there was a significant ($p<0.001$) difference in the median time from the first CTD symptom until diagnosis (diagnosis delay) between Jo-1 (median 0.4 year) versus non-Jo-1 patients (median 1 year). The non-anti-synAb control groups included 29 anti-SRP positive PM patients and 33 anti-Mi-2 positive DM patients.

Regarding the first CTD-related presenting symptom and organ manifestation, more Jo-1 patients presented with muscle or joint symptoms than non-Jo-1 patients, whereas non-Jo-1 patients were more likely to have Raynaud phenomenon as a presenting symptom (table 2). Through their disease course, Jo-1 patients had more muscle and joint involvement and less vascular and cutaneous involvement as compared with non-Jo-1 patients (table 2). A similar frequency of Jo-1 and non-Jo-1 patients reported pulmonary symptoms as the first CTD symptom and developed pulmonary fibrosis or primary pulmonary hypertension on follow-up (table 2). There was a trend seen for more frequent and severe (as measured by baseline FVC%) involvement with pulmonary fibrosis in non-Jo-1 patients. No difference in CTD-related cardiac involvement was seen in the two groups (9/120 Jo-1 patients vs 7/80 non-Jo-1 patients). The CTD diagnoses at the first UPMC evaluation for Jo-1 and non-Jo-1 patients were very different: IIM in 83% and 40%, overlap or UCTD in 17% and 43%, and SSc in 0% and 13% respectively ($p<0.001$) (table 2). While more Jo-1 patients than non-Jo-1 patients had pure PM (59% vs 23%, $p<0.001$), the frequency of DM was the same (24% vs 18%, $p=NS$). There was no difference in the average number of non-glucocorticoid immunosuppressive medications used in Jo-1 and non-Jo-1 patients (mean 1.85 (± 1.06) vs 1.44 (1.19), $p=0.19$) with methotrexate and tacrolimus used most frequently and similarly in both groups.

Mortality data in Jo-1 versus non-Jo-1 patients

Overall, 33% (66/202) of anti-synAb patients died, including 30% (36/122) of the Jo-1 and 38% (30/80) of the non-Jo-1 group at a mean age of 58 (SD 14.4) and 62 (SD 14.0) years, respectively ($p=NS$). In all, 6% (12/202) of the synthetase cohort underwent lung transplantation (seven with Jo-1 and five with non-Jo-1 anti-synAbs) at a mean age of 52

(SD 11.0) and 57 (SD 2.8) years in the Jo-1 and non-Jo-1 patients, respectively ($p=NS$). For the entire antisynthetase cohort, the 5- and 10-year unadjusted cumulative survival rates from diagnosis were 84% (95% CI 77.2% to 89.3%) and 61% (95% CI 51.1% to 69.9%), respectively. The Jo-1 patients had a significantly ($p<0.005$) better 5- and 10-year unadjusted cumulative survival from diagnosis (90% and 70%, respectively) as compared with non-Jo-1 patients (75% and 47%, respectively) (table 3). Anti-Jo-1 had a significantly better unadjusted cumulative and event free survival from diagnosis than non-Jo-1 patients ($p<0.008$, log rank test) (figure 1A,B).

The median cumulative survival time from diagnosis was longer for Jo-1 patients (15.1 years) compared with non-Jo-1 patients (9.1 years) (table 3). Similar results were seen for median event free survival time from the time of diagnosis with a median of 15 years in Jo-1 versus 8 years in non-Jo-1.

Among the patients who died, the median time to death from diagnosis was significantly longer in Jo-1 when compared with the non-Jo-1 group (6 years (IQR 2.42–10.26) vs 3 years (IQR 1.50–7.44)).

Cox proportional hazard function

The cumulative HR of non-Jo-1 patients compared with Jo-1 patients was 1.9 ($p=0.01$, CI 90%, 1.2 to 3.1) for overall survival and 1.9 ($p=0.008$, CI 90% 1.2 to 3.0) for event free survival, further demonstrating that Jo-1 patients had significantly better survival from diagnosis. Gender, ethnicity and CTD diagnosis (PM, DM, UCTD/overlap, SSc) had no influence on survival. There was a significant difference in diagnosis delay and a trend towards significance in age at first diagnosis between the two groups (table 1), and both factors were strong independent predictors of survival. After adjusting for age at diagnosis, non-Jo-1 patients demonstrated continued decreased event free survival, but with a reduced HR and significance (HR 1.6; $p=0.04$; 95% CI 1.0 to 2.7), and a trend toward decreased cumulative survival (HR 1.6; $p=0.059$; 95% CI 1.0 to 2.7). After adjusting for diagnosis delay, non-Jo-1 patients showed continued decreased survival but with a reduced HR and significance (HR 1.7, $p=0.047$, 95% CI 1.0 to 2.8) and a trend towards decreased event free survival (HR 1.6, $p=0.056$, 95% CI 1.0 to 2.6). Overall, after adjusting for age at diagnosis or diagnosis delay, the difference between cumulative survival and event free survival between the two groups was substantially diminished in both magnitude and significance.

When the interaction between the CTD diagnosis (PM, DM, overlap/UCTD, SSc) and Jo-1 groups (Jo-1 and non-Jo-1) was evaluated, non-Jo-1 PM patients demonstrated the worst cumulative survival (HR 4.5; $p=0.01$; 95% CI 1.4 to 14.6) and event free survival (HR 5.6; $p=0.004$; 95% CI 1.7 to 17.8) for all possible combinations of CTD diagnosis and Jo-1 groups, with the exception of the Jo-1 SSc group (too few patients).

Comparison of specific non-Jo-1 anti-synAb

Demographic characteristics were similar among the various non-Jo-1 autoantibody subgroups. Dyspnoea was the most common initial CTD symptom for EJ (56%), KS (50%) and PL-12 (34%) patients, while Raynaud phenomenon was the most common initial CTD symptom in 33% of PL-7 patients. Overlap or UCTD was the first diagnosis in many non-

Jo-1 anti-synAb patients (100% KS, 48% PL-12, 44% EJ and 43% PL-7), while SSc was the initial diagnosis in 23% of PL-12 patients. The median (IQR) survival times in years for the individual non-Jo-1 anti-synAb patients were the worst for EJ and PL-7 and best for PL-12 and KS (no anti-KS patients died during follow-up) (table 3). Paralleling this hierarchy of survival times, the 5- and 10-year unadjusted cumulative survival rates were worst in EJ, followed by PL-7, OJ, PL-12 and KS (table 3). Corresponding HRs for EJ and PL-7 were 4.9 (95% CI 1.9 to 12.7) and 2.5 (95% CI 1.3 to 4.6), with a p value <0.001; results for event free survival was similar.

Comparison of survival in anti-SRP and anti-Mi-2 versus anti-synAb patients

The anti-SRP and –Mi-2 control groups had a 5- and 10-year unadjusted cumulative survival from diagnosis of 85% and 68% and 92% and 80%, respectively. The 5- and 10-year unadjusted survival of both the SRP and Mi-2 control groups was better than the non-Jo-1 patients (p=0.04), but not different than the Jo-1 cohort. Similarly, the median survival time of the anti-SRP group (15.0 years) exceeded that of the non-Jo-1 group (9.1 years) but was similar to Jo-1 group (15.1 years). The median survival for the Mi-2 group could not be calculated as less than 50% patients died on follow-up (figure 2).

Cause of death

The most common causes of death for the entire antisynthetase cohort were pulmonary fibrosis in 32/66 (49%) and primary pulmonary hypertension in 7/66 (11%); however, the pulmonary cause of death was similar between Jo-1 and non-Jo-1 patients (table 4). Other causes of death are listed in table 4. For the non-Jo-1 autoantibody subsets, a pulmonary cause of death was common (EJ 3/5; PL-12 5/8 and PL-7 11/14), but two of three anti-OJ patients died of cancer.

DISCUSSION

Although the anti-synAbs have been recognised for nearly three decades and are the most common group of myositis specific autoantibodies, the clinical course and outcome of patients possessing these autoantibodies remain largely undefined. Using a prospectively collected clinical database, state-of-the-art serological testing, a retrospective EMR and NDI/SSDI query, we analysed the long term outcome and mortality of anti-synAb positive patients.

The initial CTD symptom and organ involvement varied within the synthetase cohort, as Jo-1 patients were more likely to have muscle or joint manifestation, while their non-Jo-1 counterparts most commonly had Raynaud followed by pulmonary symptoms. Although anti-synAb are classified as ‘myositis-specific,’ nearly 50% of the non-Jo-1 patients were initially diagnosed with an overlap disorder or UCTD with minimal or no evidence of myositis. Conversely, 83% of Jo-1 patients were initially diagnosed as IIM. The paucity of myopathic features at presentation confirms previous reports of the non-Jo-1 anti-synAb association with ILD in the absence of myositis.⁵⁻⁹

Overall, a third of the patients in this synthetase cohort died, with similar proportions in both Jo-1 (29%) and non-Jo-1 groups (38%). However, survival time from diagnosis was

significantly worse in non-Jo-1 patients compared with Jo-1, SRP and Mi-2 positive patients, making non-Jo-1 a poor prognosis marker. Although the cumulative survival for the entire anti-synAb cohort was similar to previously published reports,¹⁴²⁴²⁵ the non-Jo-1 patients had lower 5- and 10-year unadjusted cumulative survival rates of 75% and 47%. Non-Jo-1 patients had a significant delay in diagnosis as compared with Jo-1 patients, a key variable negatively impacting their survival. We believe this delay in diagnosis in non-Jo-1 patients is a major factor explaining the poor survival in this cohort as their atypical presentation without full-blown or classic manifestations of a discrete CTD (ie, myositis or SSc) delays both diagnosis and treatment. Other possible explanations include non-Jo-1 synthetase patients possessing etiopathogenic factors leading to more frequent and severe pulmonary fibrosis.

Although some previous reports suggest that ILD does not decrease survival in IIM patients,¹⁵²⁶ the main causes of death in our cohort were pulmonary fibrosis (49%) and primary pulmonary hypertension (11%). Pulmonary hypertension is under-recognised in patients with anti-synAbs, but should be considered when dyspnoea develops or worsens in myositis patients.²⁷ Overall, there was no difference among Jo-1 and non-Jo-1 patients in the proportion of mortality from pulmonary causes.

Several important findings emerge from these data: (1) non-Jo-1 anti-synAbs patients frequently present with nonmyositis CTD symptoms and pulmonary manifestations contributing to a diagnosis of UCTD/overlap syndromes; (2) diagnosis of a specific CTD is often delayed in patients with non-Jo-1 anti-synAbs; (3) non-Jo-1 (and Jo-1) synthetase positive patients have increased pulmonary morbidity and mortality; and (4) non-Jo-1 patients have worse survival compared with Jo-1 and non-synthetase myositis patients. Taken together, these observations have important clinical ramifications in the diagnosis and management of patients seen by both rheumatologists and pulmonologists. Specifically, non-Jo-1 anti-synAb positive patients presenting with dyspnoea and ILD as well as non-specific CTD symptoms (eg, Raynauds, mechanic hands or arthritis) likely have a delay in both diagnosis and treatment—factors that collectively contribute to poor survival.

Compounding this problem is the inability to accurately detect non-Jo-1 anti-synAbs in the sera of these patients due to less readily available, validated commercial assays. Moreover, a negative ANA may lead the managing clinician away from an autoimmune aetiology in patients presenting with ILD. The resulting delay in diagnosis and/or lack of recognition of an underlying immunological aetiology in non-Jo-1 antisynthetase patients leads to a worse outcome in patients with a potentially treatable cause of ILD. Based on these considerations, the need for high throughput, ELISA-based assessment methods of non-Jo-1 anti-synAbs is evident.

There are limitations to our study. Although we report survival statistics of the largest single anti-synAb cohort to date, the patients are from a single tertiary care centre—introducing a potential source of recruitment bias. Moreover, we are unable to draw strong conclusions regarding survival among the individual non-Jo-1 anti-synAb due to relatively small numbers in each subgroup. Given these limitations, comprehensive, multi-centre databases with longitudinal patient follow-up are necessary to fully validate our findings. Although

older serum samples are met with challenges of sample degradation, we have been performing immunoprecipitation on a routine basis for nearly 30 years, mostly close to the time of presentation at our centre. Thus, we believe that our autoantibody data are robust as evidenced by our publication record in the CTDs.^{928–30} There were similar treatment strategies employed in our CTD clinics for all patients with autoimmune ILD, and no treatment differences were noted.

In conclusion, our study emphasises the importance of considering non-Jo-1 anti-synAb in patients presenting with ILD and non-descript CTD symptoms in the absence of obvious myositis, even when screening autoantibody tests are negative. The commercial availability of more accurate testing and an increased awareness of these patients among rheumatologists and pulmonary specialists will likely lead to better patient outcomes and more thoughtful treatment strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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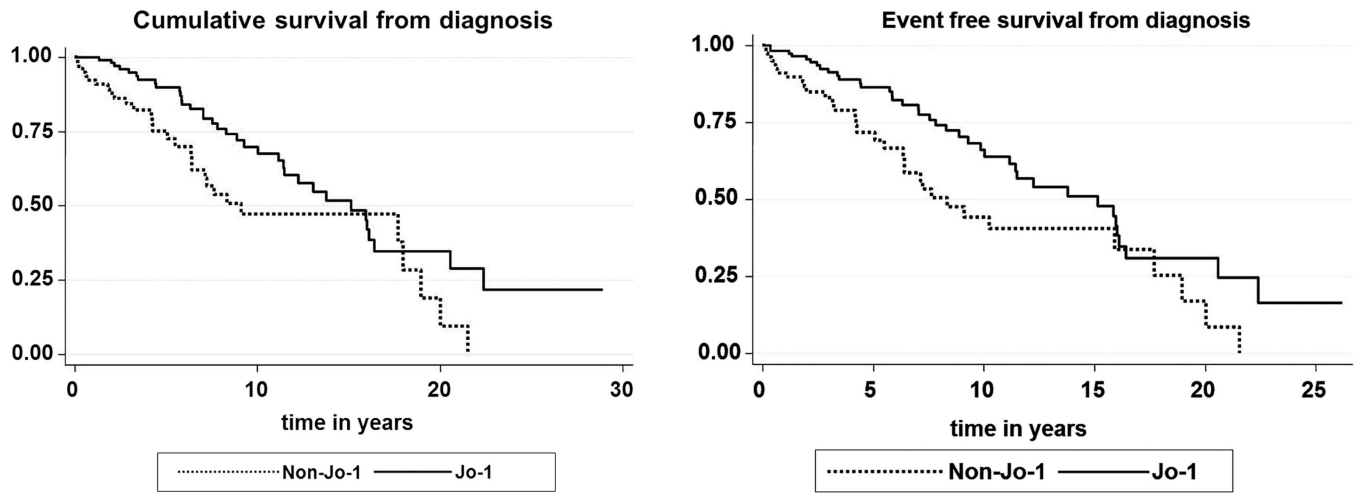


Figure 1. Kaplan–Meier curve for cumulative (A) and event free survival (B) from time of diagnosis in Jo-1 versus non-Jo-1 patients.

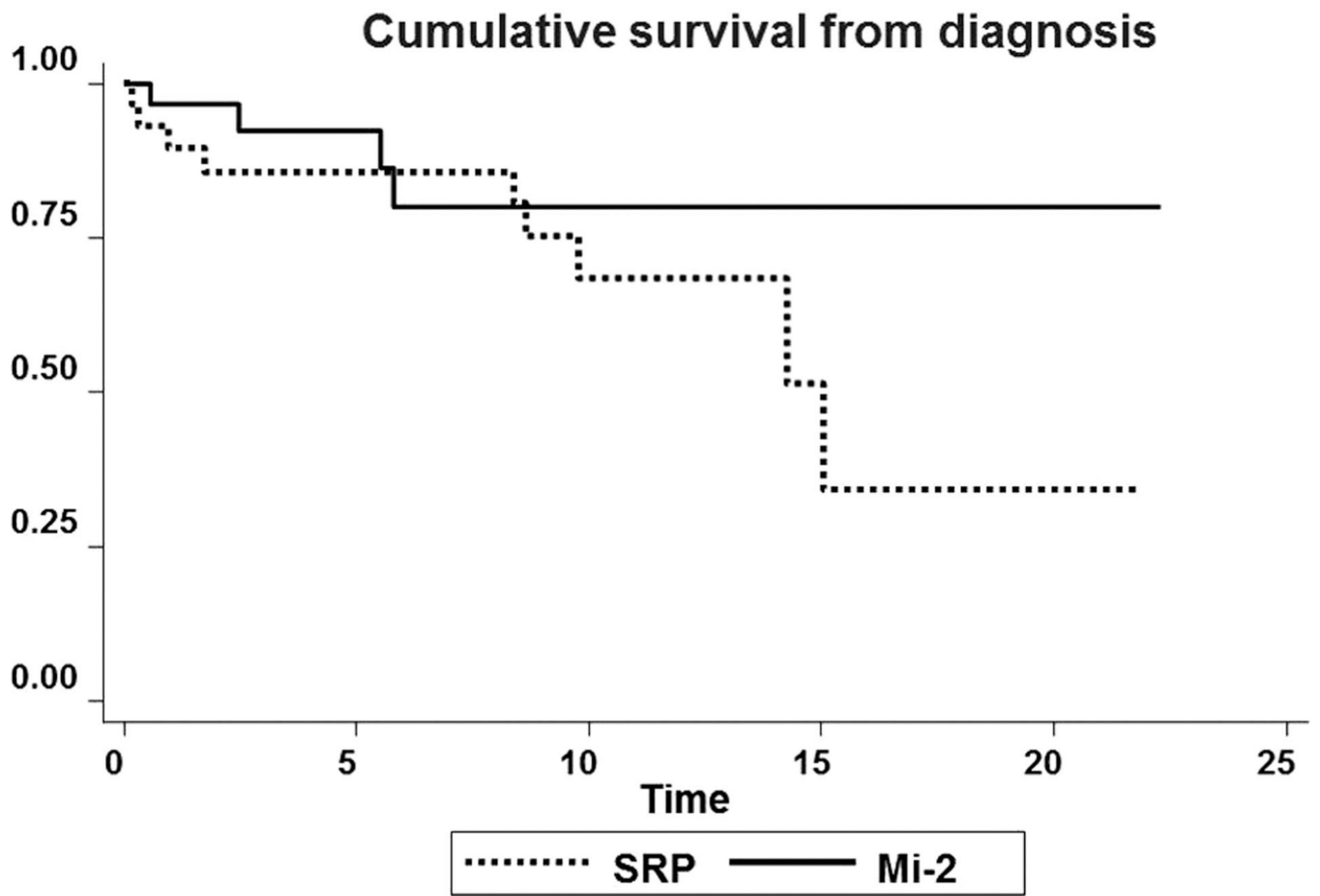


Figure 2. Kaplan–Meier curve for cumulative survival from time of diagnosis in anti-SRP versus anti-Mi-1 antibodies.

Table 1

Comparison of clinical characteristics of Jo-1 and non-Jo-1 patients

	Total cohort n=202	Jo-1 n=122 (60%)	non-Jo-1 n=80 (40%)	p Value (Jo-1 vs non-Jo-1)	SRP/Mi-2
Female	138/202 (68%)	82/122 (67%)	56/80 (70%)	0.67	40/62 (65%)
Race, % white	160/192 (83%)	100/116 (86%)	60/76 (79%)	0.23	48/62 (78%)
Tobacco use (ever)	93/200 (46%)	52/121 (43%)	41/79 (52%)	0.21	41/62 (66%)
Mean age years (SD):					
At first CTD symptom	45.1 (14.8)	44.7 (12.8)	45.8 (17.5)	0.58	
At diagnosis	47.5 (14.0)	46.0 (12.6)	49.9 (15.8)	0.05	
At first UPMC visit	49.4 (13.2)	48.3 (11.7)	51.0 (15.1)	0.15	
At lung transplant	53.8 (8.6)	51.8 (11.0)	56.6 (2.8)	0.36	
At death	59.6 (14.2)	57.7 (14.3)	61.9 (14.0)	0.24	
Median (IQR) follow-up in years (at UPMC)	2.9 (1.0–6.7)	3.4 (1.3–6.8)	2.6 (0.8–6.2)	0.3	4.6 (0.6–9.5)
CTD symptom to diagnosis (ie, diagnosis delay)	0.5 (0.3–1.7)	0.4 (0.2–0.8)	1.0 (0.4–5.1)	<0.01	0.3 (0.2–0.6)

CTD, connective tissue disease; UPMC, University of Pittsburgh Medical Center.

Table 2

First CTD symptom and first diagnosis in Jo-1 and non-Jo-1 patients

	Total cohort	Jo-1 patients	Non-Jo-1 patients	p Value (Jo-1 vs non-Jo-1)
First CTD symptom				
Muscle	47 (23.5%)	36 (30.0%)	11 (13.8%)	0.008
Joint	42 (21.0%)	32 (26.7%)	10 (12.5%)	0.016
Pulmonary	49 (24.5%)	26 (21.7%)	23 (28.8%)	0.254
Raynaud	28 (14%)	8 (6.7%)	20 (25.0%)	0.003
Fatigue	7 (3.5%)	5 (4.2%)	2 (2.5%)	0.530
Fever	5 (2.5%)	2 (1.7%)	3 (3.8%)	0.355
Rash	7 (3.5%)	4 (3.3%)	3 (3.8%)	0.875
First CTD diagnosis				
IIM	133 (65.8%)	101 (82.8%)	32 (40.0%)	<0.001
PM	90 (44.6%)	72 (59.0%)	18 (22.5%)	<0.001
DM	43 (21.3%)	29 (23.8%)	14 (17.5%)	0.287
Overlap or UCTD	59 (29.2%)	21 (17.2%)	38 (47.5%)	<0.001
SSc	10 (5.0%)	0 (0.0%)	10 (12.5%)	<0.001
Organ involvement (ever):				
Muscle	152 (75.2%)	104 (85.2%)	48 (60%)	0.001
CK (median)*		11.8 (2–42)	3.4 (0.6–10)	<0.01
Joint	128 (63.3%)	86 (70.5%)	42 (52.5%)	0.008
Pulmonary fibrosis [†]	136 (76.4%)	76 (73.0%)	60 (81.0%)	0.210
FVC% (baseline)		62.1(mean) (N=75)	56.7 (mean) (N=50)	0.070
Primary PAH	18 (14.8%)	9 (11.5%)	9 (20.9%)	0.480
Vascular	104 (53.8%)	47 (39.5%)	57 (77.0%)	0.001
Gastrointestinal	35 (17.3%)	25 (20.5%)	10 (12.5%)	0.142
Cutaneous	95 (48%)	48 (39.3%)	47 (58.7%)	0.007

* Median (IQR) of CK×time upper limit of normal.

[†] 178 had chest radiograph or CT scan to evaluate pulmonary fibrosis.

CK, creatine kinase; CTD, connective tissue disease; DM, dermatomyositis; FVC, forced vital capacity; IIM, idiopathic inflammatory myopathy; PAH, pulmonary artery hypertension; PM, polymyositis; SSc, systemic sclerosis; UCTD, undifferentiated connective tissue disease.

Table 3

Survival summary data in Jo-1 and non-Jo-1 antisynthetase patients

Survival (in years)	Jo-1	Non-Jo-1	EJ	PL-7	OJ	PL-12	KS
5-year survival from diagnosis (95% CI)	90% (81.4 to 94.7)	70% (56.9 to 79.6)	47% (12.0 to 76.3)	67% (41.8 to 82.6)	60% (12.6 to 88.2)	91% (66.2 to 97.9)	100% (no patient died)
10-year survival from diagnosis (95% CI)	75% (61.3 to 84.5)	47% (31.0 to 61.7)	*	31% (11.7 to 52.4)	*	58% (6.5 to 80.3)	100% (no patient died)
Median cumulative survival	15 years (IQR 8.3–22.4)	9 years (IQR 5.1–19.0)	1.9 years (IQR 0.2–17.7)	6.4 years (IQR 4.2–21.6)	18.0 years (IQR 0.6–18.0)	19.0 years (7.2–20.1)	* (no patient died)
Median event free survival	15 years (IQR 7.8–20.6)	8 years (IQR 4.2–19.0)					

* Too few observations to provide meaningful data.

Table 4

Cause of death in Jo-1 and non-Jo-1 patients

	All patients N=66/202	Jo-1 N=36/122	non-Jo-1 N=30/80	p Value
Pulmonary fibrosis	32 (48.5%)	16 (44.4%)	16 (53.3%)	0.511
Pulmonary HTN	7 (10.6%)	3 (8.3%)	4 (13.3%)	0.472
CTD heart disease	3 (4.6%)	2 (5.6%)	1 (3.3%)	0.666
CTD kidney disease	2 (3.1%)	2 (5.6%)	0 (0.0%)	0.190
Cancer	6 (9.3%)	4 (11.1%)	2 (6.7%)	0.532
Infection	4 (6.2%)	3 (8.3%)	1 (3.3%)	0.397
Atherosclerosis	6 (9.3%)	5 (13.9%)	1 (3.5%)	0.138
Unknown	4 (6.2%)	1 (2.8%)	3 (10.0%)	0.221

CTD, connective tissue disease; HTN, hypertension.