

Mortality in Patients with Polymyositis and Dermatomyositis in an Israeli Population

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ABSTRACT **Background:** The reported mortality rates of patients with polymyositis and dermatomyositis are highly variable worldwide. The excess mortality of patients with polymyositis/dermatomyositis has not been evaluated in an Israeli population. **Objectives:** To investigate the overall mortality in a large and well-established cohort of patients with polymyositis/dermatomyositis as compared to the mortality expected in the matched general population in a tertiary medical center. **Methods:** In this retrospective cohort study, the mortality of 166 patients with polymyositis/dermatomyositis was compared to age- and sex-matched control subjects in the general population. All-cause standardized mortality ratios (SMRs) were estimated. **Results:** Overall, 47 (28.3%) deaths were observed among patients with polymyositis/dermatomyositis during a mean follow-up period of 5.8 ± 4.8 years, which was 7 times higher than in the control group (SMR 7.4, 95% confidence interval [95%CI] 5.5–9.8). The SMRs were comparable in patients with polymyositis (7.7, 95%CI 4.8–12.3) and dermatomyositis (7.2, 95%CI 5.0–10.3). The 1-, 5-, 10-, and 15-year overall survival rates were 90.0%, 82.8%, 51.5%, and 26.1%, respectively, in patients with polymyositis, and 80.3%, 59.6%, 40.0%, and 17.1%, respectively, in patients with dermatomyositis. **Conclusions:** The overall mortality among Israeli patients with polymyositis/dermatomyositis is 7.4 times greater than for the general population. Although long-term mortality was comparable between patients with dermatomyositis and polymyositis, patients in the former group died at a notably earlier stage.

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KEY WORDS: dermatomyositis, mortality, polymyositis, standardized mortality ratio

Polymyositis and dermatomyositis are both types of idiopathic inflammatory myopathies [1], which primarily affects proximal skeletal muscle (polymyositis and dermatomyositis) and skin (dermatomyositis), but also may lead to extramuscular organ involvement, such as joints, heart, gastrointestinal tract, lungs, as well as the vascular system (manifesting as vasculitis,

pulmonary arterial hypertension, and Raynaud's phenomenon) [1,2]. Clinical presentation is heterogeneous, ranging from insidious disease with relapse and remission, to acute and even fatal progression. These diseases are systemic, characterized by the production of autoantibodies, tissue inflammation, vasculopathy, and parenchymal cell damage [3,4].

Besides the disease burden, the association of dermatomyositis and polymyositis with malignancies and interstitial lung disease makes the prognosis amongst the worst of many connective tissue diseases [5,6]. Polymyositis/dermatomyositis patients were found to experience twofold to sevenfold excess mortality as compared to their age- and sex-matched counterparts [7,8]. Although the survival of patients with polymyositis/dermatomyositis has improved since the extensive use of corticosteroids and immunosuppressants, they still have increased mortality with 5-year mortality rates of 23–73% in different cohorts originating mainly from the United States, Europe, and Japan [7,9–14]. The standardized mortality of polymyositis/dermatomyositis patients in Middle Eastern populations, and particularly in Israeli populations, however, has not been investigated. The precise evaluation of prognosis in polymyositis/dermatomyositis is hampered by the rare nature of these conditions, the lack of sufficient follow-up period, and the heterogeneous definition of previous cohorts. The prognostic outcome measures are highly variable across different cohorts.

The aim of this study was to determine the overall mortality of patients with polymyositis and dermatomyositis compared to the age- and sex-matched population of Israel.

PATIENTS AND METHODS

STUDY DESIGN AND POPULATION

This retrospective cohort study included all consecutive patients with a new diagnosis of polymyositis/dermatomyositis between 1 January 2000 and 30 June 2017 at Rambam Health Care Campus, a tertiary referral hospital in Haifa, Israel, serving a population of 1.5 million inhabitants.

Polymyositis/dermatomyositis diagnosis was made accord-

ing to the Bohan and Peter criteria [15], which consist of five components: symmetrical weakness of proximal muscles, elevation of muscle enzymes such as creatinine phosphokinase and aldolase, typical myogenic electromyographic findings, typical pathologic findings in muscle biopsy such as CD8-positive T cell infiltration in polymyositis and perifascicular atrophy in dermatomyositis, and typical dermatologic manifestations such as Heliotrope rash and Gottron sign. The presence of four or more of these five components is required to establish a diagnosis of definite dermatomyositis, while the presence of four, except dermatologic manifestations, is essential for establishing the diagnosis of polymyositis.

Cases were detected using the hospital's computerized database based on the ICD-9 diagnosis of polymyositis and dermatomyositis. Before inclusion, two of the authors (KK, MK) verified that all selected cases met all the diagnostic criteria for polymyositis/dermatomyositis and reviewed the medical files in order to exclude prevalent cases (for the incidence analysis).

Survival status and date of death of patients with polymyositis/dermatomyositis were retrieved by linking the study cohort with the National Registry of Deaths Database. Patients not listed in that database were considered survivors. All patients were followed from the onset of the disease until 30 September 2017, or until death if the latter occurred earlier during the study period.

STATISTICAL ANALYSIS

The distribution of patient's characteristics was compared between subgroups of patients using Chi-square and *t*-test for categorical and continuous variables, respectively. The observed survival curve was evaluated using the Kaplan–Meier method. The expected survival curve of the study cohort was computed according to Hakulinen's method [16], using sex-, age- (1-year classes), and calendar year-specific (1-year classes) mortality rates for the population of Israel (Israel Central Bureau of Statistics). To compare the observed and expected survival rates, we calculated standardized mortality ratios (SMRs), which is the ratio of the observed to the expected number of deaths with 95% Poisson confidence intervals. The expected number of deaths was calculated by multiplying person-years of each sex-, age-,

and calendar year-specific stratum of the study cohort by the corresponding mortality rate of the Israeli population and then summed up across all strata. All analyses were performed using STATA statistical software version 8.2 (StataCorp, College Station, TX, USA).

RESULTS

DEMOGRAPHIC DATA OF THE STUDY COHORT

The study cohort consisted of 166 consecutive patients with polymyositis/dermatomyositis. Of these patients, 104 (62.7%) were female and 62 (37.3%) were male. The mean age at diagnosis was 48.7 ± 20.5 years, and the median age was 52.6 (range 4.2–88.3). Male patients were slightly younger than female patients (45.4 ± 20.1 vs. 50.7 ± 20.6 years, respectively), although without statistical significance ($P = 0.107$) [Table 1]. In total, 84 (50.6%) patients met the diagnostic criteria of polymyositis and 82 (49.4%) met those of dermatomyositis.

Polymyositis

A total of 32 (38.1%) patients were male and 52 (61.9%) female, providing a male-to-female ratio of 1:1.6. The mean age at diagnosis was 45.3 ± 18.2 years (range 4.2–76.1, median 45.4) [Table 1]. Men were significantly younger than women at presentation (35.9 ± 17.2 vs. 51.2 ± 16.2 years, respectively, $P < 0.001$).

Dermatomyositis

Altogether, 30 (36.6%) males and 52 (63.4%) female patients were included in this subgroup, representing a male to female ratio of 1:1.7. The mean age at diagnosis was 52.2 ± 22.2 years (range 4.8–88.3, median 57.0) [Table 1]. No statistically significant difference was observed with regard to the age of presentation between male and female patients (55.7 ± 17.7 vs. 50.2 ± 24.2 years, respectively, $P = 0.280$).

Taken together, although the sex distribution was comparable between the two subgroups, patients with polymyositis were significantly younger at the onset of their disease compared to patients with dermatomyositis ($P = 0.029$).

Table 1. Characteristics of 166 patients with polymyositis and dermatomyositis follow-up from January 2000–September 2017

		Overall (n=166)	Polymyositis (n=84)	Dermatomyositis(n=82)
Age at diagnosis, years	Mean \pm SD	48.7 \pm 20.5	45.3 \pm 18.2	52.2 \pm 22.2
	Median (range)	52.6 (4.2–88.3)	45.4 (4.2–76.1)	57.0 (4.8–88.3)
Gender	% Female	62.7	61.9	63.4
Follow-up	Mean length of follow-up \pm SD, years	5.8 \pm 4.8	6.2 \pm 4.6	5.4 \pm 4.9
	Person-years time	945.3	504.5	440.8

SD = standard deviation

MORTALITY

Overall, 166 patients were followed, contributing 945.3 person-years. The mean length of follow-up was 5.8 ± 4.8 years (median 4.8 years). Table 2 presents the results of calculated SMRs stratified by sex and age group at diagnosis. Most of the deaths and the highest mortality rates (114.4 and 92.1/1,000 person-years for men and women, respectively) were observed among patients with polymyositis/dermatomyositis onset at the age of 65 and older. When compared with the expected deaths in the general population, the highest SMRs were found in patients with polymyositis/dermatomyositis onset who were younger than 45 years of age, with a value of 12.5 (95% confidence interval [95%CI], 3.1-50.2) for men and 54.5 (95%CI, 20.5-145.2) for women.

Polymyositis

Eighty-four patients contributed 504.5 person-years of follow-up. The mean length of follow-up was 6.2 ± 4.6 years.

A total of 17 (20.2%) patients died during the follow-up period. Patients who survived at the end of the follow-up were significantly younger at the time of diagnosis than those who died during the follow-up period (41.5 ± 17.3 vs. 60.5 ± 12.4 years, respectively, $P < 0.001$).

The 1-, 5-, 10-, and 15-year overall survival rates were 90.0%, 82.8%, 51.5%, and 26.1%, respectively, in the entire population of polymyositis patients [Table 3]. The median overall survival period amongst patients who died was 1.8 years (range 0.1-10.3 years).

The survival rates for patients with polymyositis were strikingly lower when compared with the general population. Kaplan-Meier survival curves for polymyositis cohort were lower than expected in the age- and sex-matched general populations, in particular as the length of follow-up increased [Figure 1].

Overall, patients with polymyositis experienced 7.7-fold the expected number of deaths (SMR = 7.7, 95%CI 4.8-12.3).

In a sex-specific analysis, the SMRs for patients with polymyositis were significantly higher for both male (SMR 9.3, 95%CI 3.0-28.9) and female patients (SMR 7.4, 95%CI 4.4-12.5).

Dermatomyositis

A total of 82 patients were followed, contributing 440.8 person-years. The mean length of follow-up was 5.4 ± 4.9 years. Thirty (36.6%) patients diagnosed in the above period died during the study period. Patients who survived at the end of the follow-up were significantly younger at the time of diagnosis than those who died (46.3 ± 23.2 vs. 62.4 ± 15.7 years, respectively, $P < 0.001$).

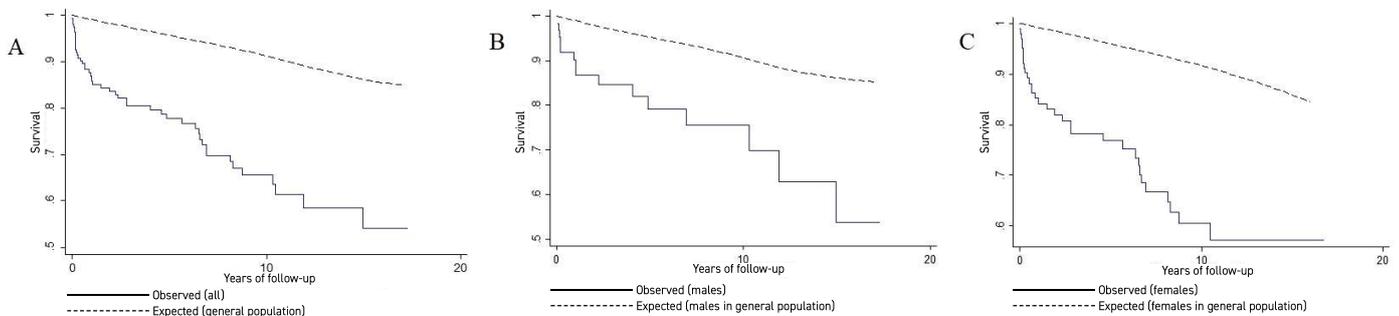
The 1-, 5-, 10-, and 15-year overall survival rates were 80.3%, 59.6%, 40.0%, and 17.1%, respectively, in the population of dermatomyositis patients [Table 3]. The median overall survival of patients who died was 1.0 year (range 0.1-15.5 years).

Relative to expected age and sex-specific overall death rates in the general population in Israel, there was a greater than 7.2-fold excess of mortality among dermatomyositis patients, with an SMR of 7.2 (95%CI 5.0-10.3) for the population of dermatomyositis patients. The excess mortality was higher in female than in male patients, with an SMR of 10.1 (95%CI 6.3-15.9) and 5.1 (95%CI 2.9-8.9), respectively.

DISCUSSION

To the best of our knowledge, our study is the first in the literature to explore the long-term mortality of polymyositis/dermatomyositis patients in Israeli patients relative to the matched

Figure 1. Observed survival curve from the onset of polymyositis/dermatomyositis was estimated using the Kaplan-Meier method. The expected survival curve of the study cohort was computed according to Hakulinen’s method using sex-, age- (1-year classes), and calendar year-specific (1-year classes) mortality rates for the population of Israel



[A] Survival among patients diagnosed with polymyositis/dermatomyositis throughout 2000-2017 compared with expected survival of the general population, **[B]** stratified analysis for polymyositis, **[C]** stratified analysis for dermatomyositis

Table 2. Observed and expected deaths and standard mortality ratios in patients with polymyositis/dermatomyositis stratified by sex and age at incidence

	Person-years	Observed deaths (rate per 1000)	Expected deaths	SMR (95%CI)
Overall	945.33	47 (49.72)	6.38	7.37 (5.53–9.80)
Males	357.31	15 (41.98)	2.69	5.57 (3.35–9.24)
< 45	189.78	2 (10.54)	0.16	12.54 (3.13–50.15)
45–64	97.61	5 (51.22)	0.51	9.79 (4.07–23.52)
≥ 65	69.92	8 (114.41)	2.02	3.95 (1.98–7.91)
Females	588.02	32 (54.42)	3.69	8.68 (6.13–12.72)
> 45	216.21	4 (18.49)	0.07	54.48(20.45–145.15)
45–64	187.19	11 (58.76)	0.57	19.29 (10.68–34.83)
≥ 65	184.62	17 (92.08)	3.04	5.56 (3.47–8.98)

95% CI = 95% confidence interval, SMR = standardized mortality ratio

Table 3. Estimated overall survival following the diagnosis of polymyositis and dermatomyositis

	1-year survival, % (95%CI)	5-year survival, % (95%CI)	10-year survival, % (95%CI)	15-year survival, % (95%CI)
Overall	82.3 (78.9–90.0)	71.3 (62.5–78.8)	44.9 (34.3–55.9)	20.7 (12.3–32.8)
Polymyositis	90.0 (81.5–94.9)	82.8 (71.1–90.4)	51.5 (35.2–67.5)	26.1 (12.6–46.5)
Dermatomyositis	80.3 (70.0–87.7)	59.6 (46.7–71.4)	40.0 (27.0–54.6)	17.1 (8.1–32.7)

95% CI = 95% confidence interval, SMR = standardized mortality ratio

general population. We demonstrated that survival in polymyositis/dermatomyositis patients was significantly lower than expected for the reference group; although we were not able to adjust for specific comorbidities, patients with polymyositis and dermatomyositis had a 7.8- and 7.2-fold increase in age- and sex-adjusted mortality relative to the general population.

The survival of polymyositis/dermatomyositis has increased substantially from a 5-year survival rate of 65% in 1971 [17] to 75–95% in subsequent studies [13,14,18]. This change may reflect the improved management approaches across the years, with corticosteroids and immunosuppressive agents contributing to the better prognosis. In our cohort, the 5-year survival rate was estimated at 82.8% and 59.6% for polymyositis and dermatomyositis, respectively, which are comparable to that reported in other studies [11,18–20], but much lower than other recently published series [13,14,21]. It was suggested that the inclusion of juvenile idiopathic inflammatory myopathies resulting in younger mean age, and the exclusion of cancer-associated patients in some of the aforementioned studies might have contributed to the lower reported mortality rates in some studies [18,21].

The assessment of the actual mortality cannot be derived only from crude mortality rates without adjusting for the expected mortality of age- and sex-matched individuals in the same region. This consideration lends weight to the calculation of SMR when investigating the mortality of the diseases. Nevertheless, this figure was estimated only in few previous studies. Our results

are consistent with a population-based study from Taiwan [8] reporting SMRs of 7.7 (95%CI 6.4–9.0) and 5.3 (95%CI 4.3–6.5) for patients with dermatomyositis and polymyositis, respectively. Despite the standardized and large sample sizes of this study, it relied on a computerized database and lacked ascertainment of included cases depending on the well-established clinical criteria [15]. Our combined SMR for polymyositis/dermatomyositis appears higher than the corresponding figures reported in Finnish (2.9, 95%CI 2.5–3.4) [7] and Spanish studies (1.6, 95%CI 1.3–1.9) [21]. Similarly, lower SMRs of 2.4 (95%CI 1.1–4.6) and 1.6 (95%CI 1.1–2.1) were estimated for patients with dermatomyositis and polymyositis, respectively, in an Australian retrospective cohort study [22].

Crude mortality rates were higher among patients whose disease onset started after 65 years of age, both among men and women. This finding is in accordance with previous reports that elderly polymyositis/dermatomyositis patients have worse outcomes compared to younger patients [14,18,19,23–25]. Nevertheless, the SMR was highest for patients with polymyositis/dermatomyositis onset before the age of 45, because the background mortality in this age category in the general population is very low.

LIMITATIONS

Because our study was conducted in a tertiary healthcare center, we may have missed mild cases of polymyositis/dermatomyositis managed by the community rheumatologists/dermatologist. However, polymyositis/dermatomyositis is uncommonly seen

in general practice, and general practitioners and community rheumatologists/dermatologists are highly unlikely to manage patients with these diseases without referring to secondary or tertiary care centers. The retrospective data collection is another obvious drawback. However, our study encompasses a relatively large sample size with an adequate follow-up period and provides novel data regarding the prognosis of these conditions in patients originating from Israel. Data regarding cause-specific mortality could not be retrieved, thus interfering with estimating the cause-specific SMRs.

CONCLUSIONS

Our retrospective cohort study reveals that the risk of all-cause mortality among Israeli patients with polymyositis/dermatomyositis is seven times greater than expected for the general population. Although long-term mortality was comparable between polymyositis (SMR 7.7, 95%CI 4.8–12.3) and dermatomyositis (SMR 7.2, 95%CI 5.0–10.3), patients with dermatomyositis experienced fatal events at an earlier stage, with the 1-year and 5-year mortality rates being estimated at 19.7% and 40.4% in dermatomyositis, and at 10.0% and 17.2% in polymyositis, respectively. This data beneficial for both physicians and patients to make decisions regarding management and surveillance.

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**There is always more goodness in the world than there appears to be,
 because goodness is of its very nature modest and retiring.**

Evelyn Beatrice Hall (1868-1956), English biographer who wrote under the pseudonym S. G. Tallentyre