Comorbidity Accrual and Mortality Rate for Patients with Giant-Cell Arteritis and Polymyalgia Rheumatica are Similar Regardless of Glucocorticoid Cumulative Dose: A Longitudinal, Retrospective Study

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Abstract

Background: Patients with giant-cell arteritis (GCA) and polymyalgia rheumatica (PMR) are treated with high cumulative glucocorticoid (GC) doses during their disease course. We sought to determine the accrual of comorbidity as well as survival in patients with GCA and PMR.

Methods: We conducted a retrospective follow-up study of an inception cohort of patients diagnosed with GCA and PMR, persistently followed at our rheumatology clinic during January 1990 - March 2018. Disease manifestations, duration of GC dose tapering and discontinuation, and mortality rate and causes were compiled. Cumulative GC dose was determined. We scored baseline and last encounter age-adjusted Charlson Comorbidity Index (CCI), Rheumatic Disease Comorbidity Index (RDCI), and CCI and RDCI increment (Δ) at last study encounter.

Results: The cohort consisted of 69 patients (24 GCA and 45 PMR, 68.1% female). Prednisone cumulative dose was $13,382.19 \pm 6189.21$ mg and $6,610.36 \pm 4,755.55$ mg for GCA and PMR, respectively, $p < 0.001$. Prednisone-free remission rate for the entire cohort was 28.9 percent for a mean follow-up period of 7.7 (range: 1-16. 9) years. The CCI and RDCI scores at diagnosis and at last study encounter did not differ between the GCA and PMR groups. Interestingly, initial prednisone dose, time to achieving 50% and 25% of initial prednisone dose, time to daily prednisone dose of 7.5mg and 5mg, as well as time to prednisone discontinuation and prednisone-free survival did not differ when comparing $\Delta CCI \geq 1$ and $RDCI \geq 1$ with $\Delta CCI = 0$ and $RDCI = 0$, respectively. Mortality rate did not differ between the GCA and PMR groups.

Conclusions: Despite significant higher cumulative doses of prednisone for patients with GCA compared to patients with PMR, comorbidity scores and mortality rate were comparable. Our results emphasize the unmet need for novel steroid-sparing drugs in PMR as well as in GCA.

Trial registration: This article reports a retrospective study and does not report results of health care intervention.

1. Background

Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) affect elderly individuals (age ≥ 50 years) and share common clinical features [1]. PMR features, mainly shoulder girdle pain and stiffness, occur in 40–60 percent of GCA patients, whereas 16–21 percent of patients with PMR have histological evidence of GCA [2, 3]. Glucocorticoids (GC) are the cornerstone of therapy in GCA and PMR [1, 2]. The recently updated recommendations of the European League Against Rheumatism (EULAR) for the management of large vessel vasculitis (LVV) [3] recommend commencing high dose GC therapy (40–60 mg/day prednisone-equivalent), and in cases of ophthalmological involvement recommend intravenous pulse therapy (e.g., 1000 mg of methylprednisolone daily for three consecutive days), followed by oral prednisone for induction of GCA remission, and gradual prednisone dose tapering, with the goal of achieving disease remission with a daily prednisone dose of ≤ 5 mg after 1 year. The doses of GC used to treat PMR are much lower than those used for treating GCA, usually initiated with a dose of 15 to

20 mg of prednisone per day followed by gradual tapering [4]. Despite the recommended goal to discontinue GC after one year [3, 4], data derived from observational studies indicate that the mean duration of GC use is approximately 2 years for PMR [2–7] with longer durations of up to 3 years for GCA [8–10]. The main cause for long-term GC treatment in GCA and PMR is the high rate of disease flare despite a gradual reduction of doses of GC [9–12]. Clinical flares have been reported to occur in more than 50 percent of patients, particularly during the first 12–16 months when the prednisone dose is reduced to ~ 5–10 mg per day, with an average of 1–2 flares per person-year [13].

Long-term treatment with GC is, however, associated with diverse adverse effects and comorbidities, such as GC-induced osteoporosis and bone fractures, cataract, diabetes mellitus, and infections as well as cardiovascular morbidity [14–19]. Indeed, it was the high prevalence of GC-induced adverse effects that led to the design of the Giant-Cell Arteritis Actemra (GiACTA) trial, which has shown that Tocilizumab treatment, an interleukin (IL)-6 receptor alpha inhibitor, was associated with a significant reduction in the cumulative prednisone dose over the 52-week trial period [20].

The purpose of this longitudinal study was to compare the prevalence and accrual of comorbidities as well as mortality in patients with GCA and PMR.

2. Methods

A single-center, retrospective longitudinal study of an inception cohort of incident patients who were diagnosed with either GCA or PMR with documented regular follow-up visits in our clinic, for at least one year during January 1990 - December 2018. The study was approved by the Institutional Review Board (0087 – 16 RMC).

2.1. Study population

The study population is comprised of incident patients who were diagnosed and persistently followed at the rheumatology clinic of Rabin Medical Center (Beilinson Hospital), a tertiary university-affiliated medical center that belongs to Clalit Health Services (CHS), the largest health maintenance organization in Israel.

GCA was diagnosed based on the American College of Rheumatology (ACR) criteria for classification of GCA [21], which require age > 50 years with two or more of the following features: (1) new localized headache, (2) temporal artery abnormality on examination, (3) erythrocyte sedimentation rate (ESR) > 40 mm/h (Westergren method), and (4) abnormal artery biopsy showing vasculitis with mononuclear cell or granulomatous inflammation, usually with giant cells. PMR was diagnosed based on the classification criteria suggested by Bird et al. [22] and the 2012 provisional EULAR/ACR classification criteria [23]. To be included in the study, patients with PMR had to fulfill the following criteria: (1) age 50 or older, (2) bilateral shoulder and/or hip girdle pain, (3) morning stiffness duration > 1 hour, (4) elevated ESR $\geq$ 40 mm/h and/or C-reactive protein (CRP) $\geq$ 0.8 mg/dl, (5) negative tests for rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (CCP), and (6) exclusion of rheumatoid arthritis or other chronic inflammatory

arthritis. Patients who had symptoms and signs of both GCA and PMR were defined as GCA for the purpose of the study.

2.2. Clinical and laboratory data collection

The electronic and/or paper charts of each patient were systematically reviewed and recorded for demographic, clinical, and laboratory features at the time of GCA or PMR diagnosis, and at each follow-up encounter especially with regard to starting or changing dosage of GC, course of GC therapy, use of steroid-sparing drugs, response to therapy, and disease flare and remission during the study period and at last encounter. The following data were reviewed with regard to GC therapy: initial oral prednisone daily dose (mg/d) and/or intravenous methylprednisolone dose; and time (months) of GC therapy until discontinuation, time required to achieve a daily prednisone dose of 50% and 25% of the initial dose, time from onset of therapy to reaching a daily prednisone dose of 7.5 mg and 5 mg, as well as time from onset of GC therapy to discontinuation. Discontinuation was defined as physician instruction for first discontinuation of GC. GC-free duration and time to first disease relapse were also recorded. The cumulative prednisone dose for each patient was calculated from the onset of GC therapy by adding the mean dose of two consecutive visits multiplied by the sum of days between the visits and the total cumulative dose.

2.3. Disease outcome

Disease outcome was assessed for the last study period encounter as follows: remission was defined as complete absence of signs and symptoms of PMR and/or GCA for at least two consecutive visits with normalization of ESR and CRP in two consecutive measurements at least 1 week apart [24, 25]. ESR value of ≤ 22 mm/hour in men or ≤ 29 mm/hour in women was considered normal regardless of age. A normal CRP was defined as a value of ≤ 0.8 mg/dl in all patients regardless of age. Disease relapse was defined as a new disease activity after a period of clinical and biological remission, or worsening disease activity that occurred during follow-up with an ESR of ≥ 29 mm/dl and/or CRP ≥ 0.8 mg/dl. When a patient had new symptoms between follow-up visits, the midpoint was chosen as the time of relapse [26].

2.4. Comorbidity

The database maintained by CHS receives continuous real-time input from pharmaceutical, medical, and administrative digital systems, and was previously used in studies on rheumatic diseases [27, 28]. Disease codes employ a modification of the International Classification of Diseases Ninth Revision (ICD-9), and medication use is coded according to the Anatomical Therapeutic Chemical (ATC) classification. The electronic charts were reviewed for clinical data represented by disease codes entered into the system by the treating family physicians and specialists including hypertension (HTN), diabetes mellitus (DM), dyslipidaemia, coronary artery disease (CAD), stroke, peripheral vascular disease (PVD), congestive heart failure (CHF), chronic kidney disease (CKD), aortic dilatation/aneurysm, acquired immune deficiency syndrome (AIDS), chronic liver disease, malignancy, dementia, cataract, chronic obstructive pulmonary disease (COPD), osteoporosis, bone fracture, peptic ulcer disease, as well as osteoarthritis and rotator cuff (RC) syndrome.

Comorbidities were scored for the time of diagnosis (first study encounter) and onset of GC therapy, and for the last study encounter using the age-adjusted Charlson comorbidity Index (aCCI) [29] and the Rheumatic Diseases Comorbidity Index (RDCI) [30]. The aCCI was designed to use extracted data from medical records, and is composed of 19 weighted comorbid conditions of which the conditions and their weightings (range 0–33) are based on the mortality risk predictive of mortality. Greater scores indicated a greater comorbid burden on the patient. The RDCI (range 0–9), is a validated, database-retrieved, comorbidity index which is composed of 11 weighted present or past comorbid conditions including pulmonary disorders (asthma/COPD, myocardial infarction (MI), other cardiovascular disease, stroke, HTN, DM, spine/hip/leg fractures, depression, gastrointestinal ulcer, other gastrointestinal disorders (liver problem, gall bladder problem, other stomach problem), and cancer [30].

Date and cause of death were recorded as indicated in the patient's electronic chart.

2.5. Statistical analysis

The statistical analysis for this paper was generated using SAS Software, Version 9.4 (by SAS Institute Inc., Cary, NC, USA). Continuous variables were presented by mean $\pm$ SD, and categorical variables by (N, %).

T-test was used to compare the value of continuous variables between study groups, and Fisher's exact test (for two groups) or Chi-square (for more than two groups) were used to compare the value of categorical variables between study groups. Survival plots were generated by the Kaplan Meier model. Hazard ratios were calculated using the Cox PH model. Two sided *p* values less than 0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics of the cohort

The study population consisted of 69 patients with either GCA or PMR (68.1% female), followed for a mean duration of 7.7 (range: 1–16.9) years. Forty-five patients were diagnosed with PMR and 24 with GCA. Mean age at diagnosis was 71.4 ± 5.6 and 74.5 ± 9.7 years for GCA and PMR, respectively. Demographic, clinical, laboratory, and pathologic findings are shown in Table 1. All GCA patients underwent temporal artery biopsy, which confirmed diagnosis in 21/24 (87.5%) of them. Nine of the PMR patients underwent temporal artery biopsy, all were negative. As expected, GCA patients more frequently presented with headache [23 (95.8%) vs. 4 (8.9%)], jaw claudication [14 (58.3%) vs. 0%] and visual disturbances [13 (54.2%) vs. 0%] compared to patients with PMR ($p < 0.001$ for each parameter), whereas PMR patients usually presented with shoulder and/or hip girdle pain and stiffness ($p < 0.001$). One (4.2%) patient with GCA was blind and 4 (16.7%) patients were diagnosed with AION at diagnosis, whereas none of the patients with PMR had disease-related visual abnormalities at the time of diagnosis. Overall, 4 (5.8%) patients had evidence of aortic dilatation/aneurysm during the disease course, although due to the early initiation of the study period (from 1990), imaging work-up for the presence of large vessel

vasculitis was not routinely performed in our population, and neither was temporal artery ultrasound performed.

Table 1
Demographics and clinical features at diagnosis

Characteristics*	GCA (n = 24)	PMR (n = 45)	All (n = 69)	<i>p</i> value
Age (years), mean	71.38	74.53	73.43	NS
Gender: female	14 (58.33)	33 (73.3)	47 (68.12)	NS
ESR (mm/h), mean	93.67	84.93	87.97	NS
CRP (mg/dl), mean	11.91	4.72	7.34	< 0.001
Shoulder/hip girdle pain & stiffness	13 (54.17)	45 (100)	58 (84.06)	< 0.001
Headache	23 (95.83)	4 (8.89)	27 (39.13)	< 0.001
Jaw claudication	14 (58.33)	0 (0)	14 (20.29)	< 0.001
Fever	5 (20.83)	7 (15.56)	12 (17.39)	NS
Weight loss	9 (37.50)	9 (20.0)	18 (26.09)	NS
Visual disturbance	13 (54.17)	0 (0)	13 (18.84)	< 0.001
AION	4 (16.67)	0 (0)	4 (5.8)	0.012
Blindness	1 (4.17)	0 (0)	1 (1.45)	
Biopsy proven				
Yes	21 (87.5)	0	21 (30.43)	
No	3 (12.5)	9 (20)	12 (17.39)	
Not done	0	36 (80)	36 (52.17)	
*Values are presented as N (%), unless otherwise stated.				
AION, anterior ischemic optic neuropathy; CRP, C-reactive protein; ESR, estimated sedimentation rate; GCA, giant cell arteritis; PMR, polymyalgia rheumatica				

3.2. GC therapy

All the patients with GCA and PMR were treated by GC (oral prednisone). Prednisone initial dose, cumulative dose, and duration of treatment are shown in Table 2. The mean initial daily prednisone dose for GCA was 61.2 ± 11.9 mg and for PMR 18.1 ± 7.8 mg ($p < 0.001$), and the prednisone cumulative dose was $13,382.2 \pm 6189.2$ mg and $6,610.4 \pm 4,755.5$ mg for GCA and PMR, respectively ($p < 0.001$). Median time duration until achieving 50% (3 months for GCA and PMR) and 25% (5.9 and 8.4 months, for GCA

and PMR, respectively) of the initial prednisone dose was not significantly different for patients with PMR and GCA. However, disease duration until achieving daily prednisone dose of 7.5 mg and 5 mg was significantly longer in the GCA group (10.7 months vs. 3.2 months, $p = 0.0002$; and 13.01 months vs. $5.03 \pm$ months, $p < 0.001$, respectively). There was a trend toward longer median time duration to the time of first discontinuation of prednisone in the GCA group compared to PMR patients, but this did not reach statistical significance (50.04 vs. 22.5 months, respectively, $p = 0.07$). However, prednisone-free survival did not significantly differ among GCA and PMR patients, nor did time to first disease flare (Table 3).

Table 2
Treatment

Treatment	GCA (n = 24)	PMR (n = 45)	<i>p</i> - value
Initial dose (mg/day)	61.25 ± 11.91 (60)	(15) 18.11 ± 7.85 (15)	< 0.001
Cumulative dose (mg)	13382.19 ± 6189.21 (10815.0)	6610.36 ± 4755.55 (5257.5)	< 0.001
Median time (months) to 50% prednisone dose	3.0084	3.0252	NS
Median time (months) to 25% prednisone dose	5.9508	8.4	NS
Median time (months) to 7.5 mg prednisone	10.6848	3.2544	0.0002
Median time (months) to 5 mg prednisone	13.01916	5.03016	< 0.001
Median time (months) to first prednisone discontinuation	50.039	22.488	0.069
MTX treatment (ever) n (%)	3 (12.5%)	1 (2.22%)	NS
Values are presented as mean ± SD (median).			
GCA, giant cell arteritis; MTX, methotrexate; PMR, polymyalgia rheumatica			

Table 3
Disease outcome

Disease outcome*	GCA (n = 24)	PMR (n = 45)	<i>p</i> - value
Duration of follow-up (years), mean ± SD (median)	7.45 ± 4.24 (6.4)	7.53 ± 4.08 (6.87)	NS
Time to first relapse (months), mean ± SD (median)	13.82 ± 10.08 (15)	11.76 ± 9.78 (10)	NS
Relapse n (%)	17 (70.83%)	32 (71.11%)	NS
Number of relapses (mean, range)	1.54 (0–7)	1.62 (0–6)	NS
Prednisone dose at relapse (mean ± SD, median)	10.44 ± 13.16 (4)	3.23 ± 2.23 (3)	0.033
GC-free survival (months), mean ± SD (median)	23.53 ± 35.03 (6.0)	20.57 ± 26.68 (8.0)	NS
GC-free remission, n (%)	7 (29.17%)	13 (28.8%)	NS
*Values are presented as n(%), unless otherwise stated.			
GC, glucocorticoids; GCA, giant cell arteritis; PMR, polymyalgia rheumatica; NS, not significant.			

3.3. Other medications

Oral weekly methotrexate as a steroid-sparing drug was prescribed in three (12.5%) patients with GCA and one (2.2%) patient with PMR ($p = 0.1$), and low-dose aspirin and statin were prescribed to 20 (83.3%) and 21 (46.7%) patients ($p = 0.004$), and to 16 (66.7%) and 33 (73.3%) patients ($p = 0.6$) with GCA and PMR, respectively. None of the patients were treated with an anti-IL-6 receptor antibody (such as tocilizumab) during the study period.

3.4. Disease remission and flare (Table 3)

During the study period, the overall GC- free remission rate in the entire cohort was 28.9%: 7 (29.17%) patients with GCA and 13 (28.8%) with PMR were observed in disease remission, indicating no statistical differences between the groups. There was no difference in mean and median GC-free survival between the GCA group [23.5 ± 35.03 (median 6) months] and PMR group [20.6 ± 26.7 (median 8) months].

During follow-up, relapse was observed in 49 (71.01%) of patients in our cohort, similar to results in both groups: 17 (70.8%) of patients with GCA and 32 (71.1%) with PMR had at least one disease relapse, with a mean time to the first relapse of 13.8 ± 10.8 months and 11.8 ± 9.8 months, and a mean number of relapses of 1.54 (range 0–7) and 1.62 (range 0–6), respectively, with no statistically significant difference between the groups. The mean and median daily prednisone dose at the first relapse for GCA was significantly higher (10.4 ± 13.2 mg; 4 mg) than for PMR (3.2 ± 2.2 mg; 3 mg), $p = 0.03$.

3.5. Comorbidities

Comorbidities for GCA and PMR patients, at diagnosis and at last encounter, are shown in Table 4. The prevalence and type of comorbidities during the follow-up period didn't differ between the GCA and PMR groups except for HTN, which was observed more commonly in PMR patients at the last study encounter ($p = 0.008$). Comorbidity burden was retrospectively scored using age-adjusted CCI and RDCI for first and last encounters, and the difference (Δ) between the last and first scores was calculated to determine the comorbidity accrual during the follow up period, as depicted in Table 5. Unexpectedly, despite the significant higher initial as well as cumulative prednisone dose in the GCA group, the mean CCI and RDCI for GCA at the last study encounter (5.75 ± 2.4 and 2.75 ± 1.5 , respectively) as well as the Δ CCI and Δ RDCI did not differ between the GCA and PMR groups. To further determine the effect of comorbidity accrual, we compared the groups according to Δ CCI ≥ 1 or no change in this score (Δ CCI or Δ RDCI = 0) during the disease course. Table 6 depicts the variables that were significantly associated with an increment of CCI ≥ 1 during disease course of our entire cohort. Of note, diagnosis of either GCA or PMR was not associated with an increment of CCI during follow-up period. CAD ($p = 0.04$), and DM ($p = 0.04$) at the last encounter were significantly associated with an increase in CCI during the follow-up period, while dyslipidemia tended to increase CCI ($p = 0.06$). Prednisone daily dose at initiation of GC therapy, cumulative GC dose, as well as time until achieving 50% and 25% of initial dose, time to taper off of daily prednisone dose to 7.5 mg and 5 mg, and time to GC discontinuation were not associated with accrual of comorbidity (Δ CCI ≥ 1) during disease course. However, patients who had a disease relapse had a significantly higher CCI at the end of the follow-up period: Δ CCI ≥ 1 : 1.81 ± 1.58 vs. Δ CCI = 0: 0.88 ± 1.09 , $p = 0.03$. Neither low-dose aspirin and statins nor weekly oral methotrexate had a protective effect on accrual of comorbidity during the study period.

Table 4
Comorbidities at diagnosis/last encounter

Comorbidities*	GCA	GCA	PMR	PMR	All	All	<i>p</i> last
	Diagnosis	Last visit	Diagnosis	Last visit	Diagnosis	Last visit	
HTN	12 (50)	15 (62.5)	29 (64.44)	41 (91.11)	41 (59.42)	56 (81.16)	0.008
Diabetes	3 (12.5)	8 (33.33)	8 (17.78)	18 (40.0)	11 (15.94)	26 (37.68)	NS
Dyslipidemia	14 (58.33)	18 (75.0)	22 (48.89)	37 (82.22)	36 (52.17)	55 (79.71)	NS
IHD	6 (25)	12 (50)	9 (20)	15 (33.33)	15 (21.74)	27 (39.13)	NS
Stroke	3 (12.5)	4 (16.67)	2 (4.44)	3 (6.67)	5 (7.25)	7 (10.14)	NS
PVD	1 (4.17)	3 (12.5)	3 (6.67)	7 (15.56)	4 (5.8)	10 (14.49)	NS
Malignancy	3 (12.5)	7 (29.17)	11 (24.44)	12 (26.67)	14 (20.29)	19 (27.54)	NS
Cataract	7 (29.17)	19 (79.17)	10 (22.22)	32 (71.11)	17 (24.64)	51 (73.91)	NS
Osteoporosis	4 (16.67)	6 (25)	10 (22.22)	19 (42.22)	14 (20.29)	25 (36.23)	NS
Osteoporotic # ever		3 (12.5)		7 (15.56)		10 (14.49)	NS
CHF	0 (0)	2 (8.33)	2 (4.44)	5 (11.11)	2 (2.90)	7 (10.14)	NS

*Values are presented as N (%), unless otherwise stated.

CHF, congestive heart failure; HTN, hypertension; IHD, ischemic heart disease; IVD, ischemic vascular disease; PMR, polymyalgia rheumatica; PVD, peripheral vascular disease; NS, not significant.

Table 5
Comorbidity scores

Comorbidity score*	GCA (n = 24)	PMR (n = 45)	All (n = 69)	<i>p</i> -value
CCI				
At diagnosis	3.79 ± 1.93 (3.0)	4.2 ± 1.98 (4.0)	4.06 ± 1.96 (4.0)	NS
Last	5.75 ± 2.4 (5.5)	6.38 ± 2.4 (5.0)	5.35 ± 2.51 (6.0)	NS
Δ	1.96 ± 1.49 (2.00)	2.18 ± 1.68 (2.0)	2.1 ± 1.61 (2.0)	NS
RDCI				
At diagnosis	1.58 ± 1.5 (1.0)	1.69 ± 1.46 (2.0)	1.65 ± 1.46 (1.0)	NS
Last	2.75 ± 1.54 (3.0)	2.82 ± 1.37 (3.0)	2.80 ± 1.42 (3.0)	NS
Δ	1.17 ± 1.01 (1.0)	1.13 ± 1.08 (1.0)	1.14 ± 1.05 (1.0)	NS
*All values are presented as mean ± SD (median).				
CCI, Charlson comorbidity index; GCA, giant cell arteritis; PMR, polymyalgia rheumatica; RDCI, Rheumatic diseases Comorbidity Index; NS, not significant.				

Table 6
Comorbidity accrual ($\Delta CCI \geq 1$) during disease course of GCA and PMR cohort

	$\Delta CCI = 0$ (n = 16)	$\Delta CCI \geq 1$ (n = 53)	<i>p</i> value
GCA/PMR	5 (20.8%)/ 11 (24.4%)	19 (79.2%)/ 34 (75.6%)	NS
Age at diagnosis (years)	71.4 $\pm$ 6.7	74.06 $\pm$ 9.03	NS
Initial GC dose (mg/d)	32.2 $\pm$ 22.9	33.4 $\pm$ 22.9	NS
Time to 50% initial GC dose (months)	4.5 $\pm$ 2.6	3.2 $\pm$ 1.3	NS
Time to 25% initial GC dose (months)	10.1 $\pm$ 8.7	8.5 $\pm$ 7.9	NS
Time to daily GC dose 7.5 mg (months)	6.7 $\pm$ 3.9	5.9 $\pm$ 3.6	NS
Time to daily GC dose 5 mg (months)	10.6 $\pm$ 8.9	8.6 $\pm$ 7.2	NS
Time to GC discontinuation (months)	29.7 $\pm$ 16.2	22.9 $\pm$ 7.3	NS
Number of relapses	0.9 $\pm$ 1.1	1.8 $\pm$ 1.6	0.03
DM at last encounter	2 (12.5%)	22 (41.5%)	0.04
Dyslipidemia at last encounter	2 (12.5%)	22 (41.5%)	0.06
Statin use ever	8 (50%)	33 (62.3%)	0.06
CAD at last encounter	2 (12.5%)	23 (43.4%)	0.04
Aspirin use ever	8 (50%)	33 (62.3%)	NS
*Values are presented as mean $\pm$ SD or n (%).			
CAD, coronary artery disease; CCI, Charlson comorbidity index; DM, diabetes mellitus; GC, glucocorticoids (daily prednisone), GCA, giant cell arteritis; NS, not statistically significant; PMR, polymyalgia rheumatica; NS, not significant.			

Cox regression analysis of the hazard ratio (HR) for acquiring ΔCCI of at least 1 point, showed that atherosclerotic cardiovascular diseases (CVD) and the risk factors for CVD at the time of diagnosis were significantly associated with increment in comorbidity score at the last study encounter ($\Delta CCI \geq 1$) (Table 7). Diagnosis of PMR was not associated with increment in comorbidity score. However, longer duration of GC-free survival was significantly associated with lower HR for $\Delta CCI \geq 1$ (HR 0.5, $p = 0.03$). Older age and CVD manifestations such as CAD, stroke, and CHF at diagnosis were significantly associated with greater HR for $CCI \geq 1$ at the last study encounter, as well as risk factors at the time of diagnosis and evidence of aortic dilatation/aneurysm. Of interest, one (4.17%) patient with GCA was diagnosed with adrenal hypofunction at the last encounter that was attributed to prolonged GC treatment.

Cox regression analysis showed that hypoadrenalism was significantly associated with a greater risk for comorbidity accrual during the study period (HR9.32, 95% CI 1.53–56.77, $p = 0.015$).

Table 7
Univariate analysis (COX regression) for $\Delta CCI \geq 1$ risk factors

Parameter	Hazard ratio	95% Confidence interval	<i>p</i> value (chi square)
Age at diagnosis (years)	1.06	1.006–1.1	0.02
PMR diagnosis	1.16	0.675–2.005	0.58
HTN at diagnosis	1.91	1.06–3.45	0.03
DM at diagnosis	2.61	1.23–5.52	0.01
Dyslipidemia at diagnosis	3.67	1.91–7.08	< 0.0001
CAD at diagnosis	2.01	1.07–3.79	0.03
Stroke at diagnosis	2.88	1.13–7.29	0.03
CHF at diagnosis	6.93	1.77–27.07	0.005
Aortic disease at last encounter	4.51	1.18–17.19	0.03
Tobacco smoking (current)	3.3	1.26–8.67	0.015
Hypoadrenalism	9.32	1.53–56.77	0.015
GC-off duration	0.99	0.98–0.99	0.03
CAD, coronary artery disease; CHF, congestive heart failure; DM, diabetes mellitus; GC, glucocorticoids; HTN, hypertension; PMR, polymyalgia rheumatica			

3.6. Mortality

During the study follow-up period, 3 (12.5%) patients with GCA and 8 (17.7%) with PMR died. The 5-, 10- and 15-years survival for GCA and PMR in our cohort were 62.5 and 71.1 percent; 25 and 24.4 percent; and 8.3 and 4.4 percent, respectively, with no significant difference between the GCA and PMR groups (Fig. 1). As depicted in Table 8, univariate analysis shows that a higher HR for mortality was significantly associated with older age (HR 1.1, 95% CI 1.02–1.22, $p = 0.02$), DM (HR 4.15, 95% CI 1.033–16.73, $p = 0.04$), PVD (HR 8.1, 95% CI 2.1–31.07, $p = 0.002$), CHF (14.7, 95% CI 1.9–113.3, $p = 0.009$), malignancy (HR 3.9, 95% CI 1.11–14.05, $p = 0.03$), and stroke (HR 12.97, 95% CI 3.43–49.0, $p = 0.0002$) at diagnosis were positively correlated with higher risk of death, and this association was also observed for IHD (HR 2.99, 95% CI 0.8–10.65, $p = 0.09$) and COPD (HR 5.9, 95% CI 0.93–38.41, $p = 0.06$), although not statistically significant. GC initial dose as well as cumulative dose and treatment duration were not associated with increased risk of death in our cohort.

Table 8
Univariate analysis (COX regression) for death risk factors

Variable	Hazard Ratio	95% CI	<i>p</i> -value
Diagnosis PMR	1.7	0.388–7.522	0.47
Gender Male	1.017	0.268–3.854	0.98
Age at diagnosis	1.1	1.018–1.219	0.018
Initial prednisone dose	0.99	0.961–1.020	0.5
Cumulative dose	1.0	1.0–1.0	0.0561
No. of flares	0.728	0.452–1.172	0.19
HTN at diagnosis	1.285	0.362–4.562	0.69
DM at diagnosis	4.157	1.033–16.727	0.0449
PVD at diagnosis	8.1	2.1–31.07	0.002
CHF at diagnosis	14.7	1.9–113.3	0.009
Malignancy at diagnosis	3.9	1.11–14.05	0.03
IHD at diagnosis	2.993	0.841–10.656	0.0905
COPD at diagnosis	5.9	0.93–38.41	0.06
Stroke at diagnosis	12.971	3.433–49.010	0.0002
RDCI at diagnosis	1.695	1.185–2.425	0.0038
CCI at diagnosis	1.879	1.339–2.637	0.0003
CCI last	1.356	1.105–1.665	0.0036
RDCI last	1.536	0.975–2.420	0.0642
Delta RDCI + 1	0.59	0.167–2.087	0.41
Delta CCI + 1	0.195	0.007–5.233	0.3297
CCI, Charlson comorbidity index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease; PVD, peripheral vascular disease; PMR, polymyalgia rheumatica; RDCI, Rheumatic diseases comorbidity index			

Higher comorbidity scores [CCI at diagnosis and last encounter (HR 1.9, 95% CI 1.34–2.64, $p = 0.0003$, and HR 1.356, 95% CI 1.1–1.7, $p = 0.0036$, respectively) and RDCI at diagnosis (HR 1.7, 95% CI 1.2–2.4, $p = 0.004$)] were significantly associated with higher risk of death (Table 9). Neither $\Delta\text{CCI} \geq 1$ nor $\Delta\text{RDCI} \geq 1$ were significantly associated with increased risk of death.

4. Discussion

Our detailed and comprehensive database of an inception cohort of patients with GCA and PMR followed in a rheumatology clinic for a median period of 6.46 years was used to compare the rate and risk of comorbidity and mortality of patients with GCA and PMR, as well as analyze disease outcome with respect to GC therapy. Our data suggest that accrual of comorbidities, defined as ΔCCI or $\Delta RDCI \geq 1$, as well as the mortality rate did not differ despite the significantly higher initial and cumulative dose of prednisone in the GCA group compared to the PMR group.

Nevertheless, accrual of comorbidities during the study period defined as $\Delta CCI \geq 1$ was significantly associated with atherosclerosis CAD and DM, as well as higher number of disease relapses (Table 7). Of note, neither aspirin nor statin use had a protective effect with respect to accrual of comorbidities in our cohort of patients with GCA and PMR.

Although the rate of mortality was not significantly different in the GCA and PMR groups, Cox regression analysis showed that older age, CAD, stroke, CHF, and aortic dilatation/aneurysm were significantly associated with an increased risk of mortality; in addition to HTN, DM, dyslipidemia and tobacco smoking that are all known to be associated with atherosclerotic CVD. Adrenal hypofunction diagnosed during the follow up period, which probably is a result of long-term GC treatment, was significantly associated with higher risk of death.

GC is the cornerstone treatment for both GCA and PMR with median treatment duration of 2–3 years [1–10]. GC-related adverse effects are common and have not changed since GC was first used for managing GCA/PMR [5, 6, 8]. A population-based study of incident GCA cases derived from the Rochester Epidemiology Project between 1950 and 2009 has shown that GC adverse effects (excluding HTN, dyslipidemia and cataract), were recorded in 95 percent of patients with no difference in the risk of developing adverse effects for patients diagnosed in later years (1980–2009) compared to earlier years of GC therapy (1950–1979) [8]. A nested case-control analysis of serious GC-related adverse effects found that a trend of increasing risk of DM and osteoporosis was associated with increasing cumulative prednisolone dose; higher average daily dose (30 mg/d) was associated with an increased risk of DM, osteoporosis, fractures, glaucoma, serious infection, and death compared with lower dose (5 mg/d) [17]. A prospective study of patients with GCA and PMR using the National Database of the German Collaborative Arthritis Centers has shown that of the examined comorbidities, only osteoporosis was observed at increased rate within 3 years and that persistent disease activity within the first year was a good predictor of long-term GC therapy [19]. Moreover, previous studies including five randomized controlled trials [13–15], failed to demonstrate a significant association between GC dose and the development of adverse effects. Our results are in accordance with studies showing no correlation between either initial daily GC dose or cumulative GC dose with risk of developing GC-related adverse effects or comorbidities. However, other studies have shown association of adverse effects with a higher GC cumulative dose [11]. A recent retrospective study showed that each 1000 mg increase GC cumulative dose exposure was associated with an increase of HR for GC-related adverse effects by three percent [12]. Moreover, our data suggest that despite a significant difference in the initial and cumulative GC dose in patients with GCA compared to PMR, the risk of developing adverse effects are similar in GCA and PMR.

Petri et al. [31] have also performed a retrospective analysis of GCA patients, and described comorbidities associated with GCA, including several related to GC use. Their data was based on the UK clinical practice research datalink, a database that reflects primary care. In contrast, our study only included patients diagnosed by a rheumatologist and followed up for at least one year at our rheumatology clinic.

To assess comorbidity accrual in GCA and PMR during the disease course, we've scored the comorbidities at the time of diagnosis and at end of the follow-up period using the age-adjusted CCI [29] and RDCI [30], and calculated the Δ CCI and Δ RDCI as comorbidity accrual scores (Table 5). Neither diagnosis of GCA or PMR and patient's age, nor GC cumulative dose or GC treatment duration, were associated with increase of comorbidity scores during the study follow-up period, but disease flare as well as DM and CAD were significantly associated with a greater CCI at the end of this period.

Our results of similar comorbidity and mortality rate in GCA and PMR patients despite the significant higher prednisone initial, as well as significantly higher cumulative dose in the treatment of GCA compared to PMR, raised concerns about the outcome and GC-related adverse effects in patients with PMR. PMR is the most prevalent chronic inflammatory disease of the elderly [1, 14, 15, and 32]. To date, GC remains the main therapy for PMR [19, 33] and other conventional treatments such as methotrexate have not shown significant benefits in ameliorating disease symptoms and reducing GC-related adverse effects [34, 35].

Survival rate in our cohort was similar for patients with GCA and PMR. Mortality was positively correlated with atherosclerotic CVD, such as CAD, stroke, and aortic dilatation/aneurysm, as well as the presence of known risk factors for atherosclerosis such as HTN, DM, dyslipidemia and smoking. Moreover, higher CCI and RDCI at diagnosis and higher CCI at the last study encounter were associated with increased risk of mortality. GC cumulative dose was not associated with higher risk of death in our cohort (Table 8). Recent studies seeking associations between GCA, PMR and CVD [38], including a meta-analysis [39], did not find evidence of increased risk of CAD in patients with GCA compared to the non-GCA population. A population-based longitudinal study comparing 12 CVDs in patients with and without GCA and/or PMR did not find an increased risk of CVD [40]. Previous studies have shown that the mortality rate of patients with GCA [41–43] and PMR [44] is similar to the age-matched general population. Nevertheless, our findings showing an increased risk of death in patients who had evidence of CAD, stroke, DM, and HTN at the time of diagnosis of GCA or PMR emphasize the importance of controlling CVD in this patient population. Indeed, our results are in line with recent population-based studies that suggest increased prevalence of CVD as a leading cause of death in GCA and/or PMR [41–45]. Moreover, this is the first study to demonstrate increased risk of death in patients with PMR as well as GCA with higher comorbidity (CCI and RDCI) score.

Recently, Tocilizumab was approved for the treatment of GCA following the GiACTA study that showed superiority of tocilizumab combined with prednisone compared to prednisone alone in achieving sustained remission at one year [20]. Several studies have shown that either tocilizumab monotherapy [36], or in combination with prednisone [37], are effective in controlling PMR symptoms. Our data suggest

that disease relapse was significantly associated with comorbidity accrual during the disease course as well as increased risk of death of patients with PMR or GCA, and thus warrant randomized controlled trials in the effort to find biologic therapies to improve disease outcome and ameliorate GC-related adverse effects as well as atherosclerotic vascular comorbidity in patients with PMR similar to GCA.

Our study has some limitations inherent with its retrospective design and relatively small cohort. On the other hand, this study has certain strengths. First, we analyzed a population that has been diagnosed and followed continuously by rheumatologists in a single center for a median duration of 14.5 years. Second, the CHS database as well as the electronic charts establish a continuous comprehensive documentation of long-term real-life data made by all the physicians involved in medical care of the patients through the entire life span, thus allowing us to derive reliable data on disease course and outcome, GC therapy dose and duration, that allow us to compare end points between the GCA and PMR groups.

Conclusions

Regardless of GC cumulative dose and treatment duration, the rate accrual of comorbidities as well as the risk of death does not differ between GCA and PMR.

List Of Abbreviations

American College of Rheumatology (ACR); anti cyclic citrullinated peptide (anti-CCP); Clalit Health Services (CHS); C-reactive protein (CRP); estimated sedimentation rate (ESR); European League Against Rheumatism (EULAR); glucocorticoids (GC); giant cell arteritis (GCA); giant-cell arteritis actemra (GiACTA); interleukin (IL); large vessel vasculitis (LVV); polymyalgia rheumatica (PMR); rheumatoid factor (RF)

Declarations

Ethics approval and consent to participate:

The study was approved by the Institutional Review Board (0087-16 RMC).

Consent for publication:

Not applicable

Availability of data and materials:

The crude data of the study will be available from corresponding author upon request.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

EPS and ADL participated in data retrieval and analysis. EPS was a major contributor in writing the manuscript. YM initiated the study. . All authors read and approved the final manuscript.

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Figures

Figure 1

Survival probability Kaplan-Meier curve for survival of our cohort of 69 patients with PMR or GCA,during mean follow-up period of 7.7 (range: 1-16. 9) years