Mortality among Patients with Giant Cell Arteritis: A Large-scale Population-based Cohort Study

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ABSTRACT. ***Objective.*** Studies regarding mortality among patients with giant cell arteritis (GCA) have yielded conflicting results. Thus in this large population-based study we aimed to examine whether GCA is associated with increased mortality, and if so, the effect of age at diagnosis and sex on the association.

Methods. We used the medical database of Clalit Health Services for this retrospective cohort study. Followup was from January 1, 2002, and continued until death or end of followup on September 1, 2018. Incident GCA patients were compared with age- and sex-matched controls. Estimated median survival times were calculated using the Kaplan-Meier method. HR for all-cause mortality were obtained by the Cox proportional hazard model, adjusted for sociodemographic variables and cardiovascular risk factors.

Results. The study included 7294 patients with GCA and 33,688 controls. The mean age at start of followup was 72.1 ± 9.9 years with 69.2% females. Estimated median survival time was 13.1 years (95% CI 12.6–13.5) in patients with GCA compared with 14.4 years (95% CI 14.1–14.6) in controls ($p < 0.001$). The multivariate analysis demonstrated increased mortality risk in the first 2 years after diagnosis (HR 1.14, 95% CI 1.04–1.25) and > 10 years after diagnosis (HR 1.14, 95% CI 1.02–1.3). The mortality risk was higher in patients diagnosed at ≤ 70 years of age [HR 1.5 (95% CI 1.14–1.99) 0–2 yrs; HR 1.38 (95% CI 1.1–1.7) > 10 yrs].

Conclusion. Patients with GCA have a minor decrease in longterm survival compared to age- and sex-matched controls. The seen difference is due to excess mortality in the first 2 years, and > 10 years after diagnosis. Patients diagnosed ≤ 70 years of age are at greater risk. (First Release July 1 2020; J Rheumatol 2020;47:1385–91; doi:10.3899/jrheum.190927)

Key Indexing Terms:
GIANT CELL ARTERITIS TEMPORAL ARTERITIS VASCULITIS
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Giant cell arteritis (GCA) is the most prevalent vasculitis over the age of 50, affecting large- and medium-size arteries[1]. The arteries most commonly involved are the aorta and its major branches, as well as the superficial temporal, ophthalmic, posterior ciliary, and the vertebral arteries[2]. GCA only rarely occurs before the age of 50 and reaches a peak incidence in the eighth decade of life[3]. The highest incidence rates have been reported from Scandinavian countries, ranging between 19.1 and 32.8 per 100,000 for populations older than 50 years[3]. In Spain, the Mediterranean region, Canada, and Israel, reported GCA incidence rates range between 6.9 and 11.3 per 100,000 individuals over the age of 50[3,4].

A common and dangerous complication of GCA is partial or complete loss of vision, occurring in 20% of patients, often early in the course of the disease[5,6]. Another major complication is large-vessel involvement, which may lead to aortic dissection or aneurysm. The leading cause of death

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in patients with GCA is cardiovascular (CV) disease (39%), followed by cerebrovascular disease (14%) and infections (13%)[5].

The mortality of patients with GCA has long been a subject of debate. Several studies have addressed this issue, yielding conflicting results. Most studies reported no difference in mortality patterns among patients with GCA compared to the general population[6–16]. However, several others reported increased mortality in the first 2 years following diagnosis and among patients diagnosed after 70 years of age[7,10,17,18,19]. Increased longterm mortality has also been observed[17,18,20]. Most of these studies had considerable limitations, such as small sample size, lack of matched comparison cohorts, and hospital setting.

To deal with these limitations, we conducted a large, nationwide, population-based cohort study. To further isolate GCA as the cause for mortality, we used a multivariate model considering sociodemographic variables and CV risk factors found to be associated with GCA.

MATERIALS AND METHODS

Data source. Data were obtained from the comprehensive, electronic database of Clalit Healthcare Services (CHS). CHS is the largest health maintenance organization in Israel and serves about 4.4 million insured members (over 50% of Israel's population) from heterogeneous ethnic groups and has continuous real-time input from pharmaceutical, medical, and administrative operating systems. The database was designed for purposes of administrative and clinical management and is available for use in epidemiological studies. The database is undergoing a process of diagnosis validation by logistic checks (such as matching the diagnoses from different sources). The CHS database was used in several studies before including those addressing patients with GCA[21,22,23,24,25,26], and was demonstrated to have high validity of diagnoses for chronic diseases and for diseases from the rheumatology field[27,28,29,30]. For our study, the information drawn from the database has been input continuously since computerized systems were first used in CHS, from around January 1, 2002, to September 1, 2018 (Figure 1).

Population and design. This study was designed as a retrospective cohort study comparing incident GCA cases to age- and sex-matched controls without the diagnosis of the disease. The GCA cohort included all patients with at least 1 documented diagnosis of GCA (International Classification of Diseases, 9th revision code 446.5), made in primary care centers, in- and outpatient clinics, or hospitalization discharge letters, between January 1, 2002, to December 31, 2017. Patients who were under the age of 50 years at the time of the first diagnosis and patients who had a recorded diagnosis of GCA before January 1, 2002, were excluded. Controls were age- and sex-matched and included patients without a recorded diagnosis of GCA, randomly assigned from the CHS electronic database. Followup for patients with GCA started at the date that the first recorded diagnosis of GCA was made (index date), and for the controls at the index date of their matched patient with GCA. Followup continued until the earliest of the following: death (event) or end of study followup on September 1, 2018 (censored cases).

Study variables. For each subject, age, sex, and socioeconomic status (SES) at the beginning of followup were obtained from their CHS medical record. SES was defined according to the poverty index of the member's residence as defined during the 2008 national census. The poverty index is based on several variables, including household income, education, crowding, material conditions, and car ownership. The score ranges from 1 to 20, based on cluster analysis, with 1 being the lowest SES and 20 the highest. In our study, these layers were divided into tertiles (low, medium, and high). Prevalence of hypertension (HTN), diabetes mellitus, dyslipidemia, and smoking prior to index date were also obtained from the CHS chronic disease registry, which was demonstrated to have 90–100% degree of accuracy[27]. These variables were dichotomized.

Statistical analysis. Differences in baseline characteristics between different groups of independent variables were compared using t test or

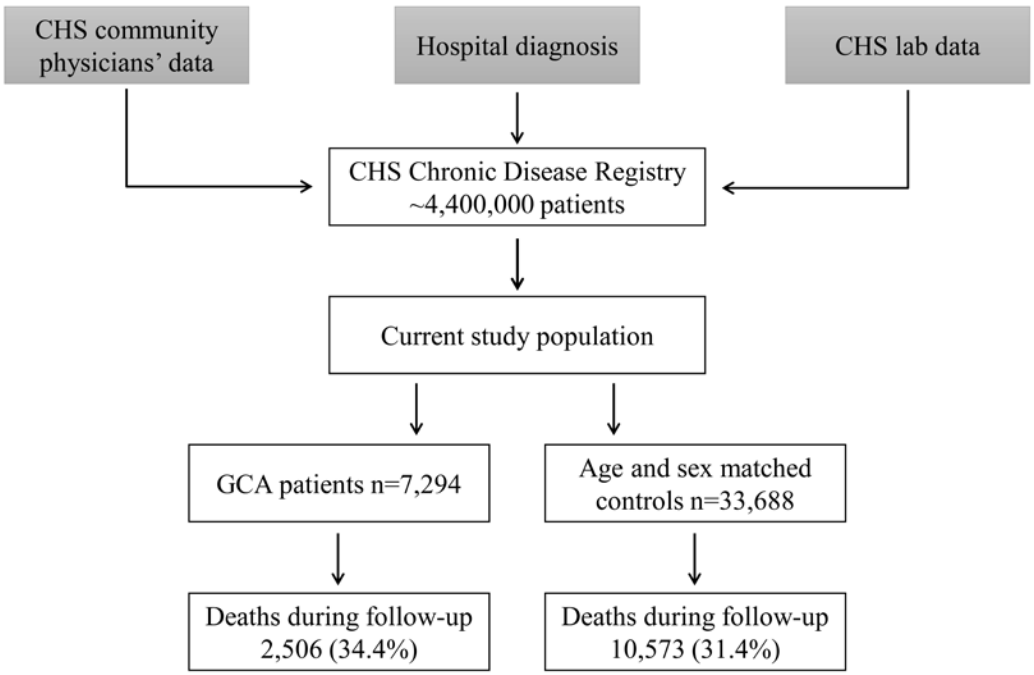

Figure 1. Study population. CHS: Clalit Healthcare Services; GCA: giant cell arteritis.

Mann-Whitney U test for continuous variables, and chi-2 test for categorical variables. Analysis was performed in 3 different followup periods according to the time from diagnosis: 0–2 years, 2–10 years, and over 10 years. This division was used in previous studies[31] and is based on the clinical course of GCA, which includes exacerbations that occur mainly during the first 2 years after diagnosis[32,33], and large-vessel complications that reach a peak incidence rate late in the course of the disease[34].

Mortality rates (MR) are presented as the number of deaths per 1000 person-years (PY) and were calculated by dividing the number of deaths in a specific stratum with the sum of PY of that stratum. Survival analysis was performed using Kaplan-Meier method with a posthoc log-rank comparison of patients with GCA and controls. The analysis was for the entire followup period (~16 yrs). Death from all causes was considered as an event and patients who were alive at the end of the study followup were considered censored cases.

Multivariate survival analysis was conducted using the Cox proportional hazard model. Death from all causes was considered an event. HR were calculated comparing GCA and non-GCA subjects. The model accounted for age, sex, smoking, SES, HTN, dyslipidemia, and diabetes. We repeated the analysis for the 3 followup periods (0–2 yrs, 2–10 yrs, and > 10 yrs) and for different subgroups based on the age at diagnosis (≤ 70 or > 70 yrs) and sex.

Statistical analysis was performed using the SPSS for Windows, V.23.0 (IBM SPSS Statistics), and WINPEPI (PEPI-for-Windows V11.65, a statistical program for epidemiologists).

Ethics. This study was approved by the CHS Ethics Committee in Tel Aviv, Israel (Approval number 0212-17-COM). No informed consent was needed (existing database).

RESULTS

Cohort characteristics. The study population consisted of 40,982 subjects, of whom 7294 were patients with GCA and 33,688 were age- and sex-matched controls who were not diagnosed with the disease. The mean age of the entire cohort at the beginning of the followup was 72.0 ± 9.9 years (median 72.8 yrs), and 69.3% were women. Among patients with GCA, 13.7% (996) were diagnosed at ages 50–59 years, 24.9% (1816) at ages 60–69 years, 37.1% (2706) at ages 70–79 years, and 24.3% (1776) after the age of 80 years. A minor statistically significant difference in the age of enrollment was observed. This difference has no clinical significance and occurred because of the large sample size, and because the matching was done based on the patients' ages in years. No statistically significant difference was found in SES between groups. GCA-diagnosed patients had a significantly higher prevalence of the traditional CV risk factors (smoking, diabetes, HTN, and dyslipidemia) than did controls ($p < 0.001$; Table 1).

MR differences. During the entire followup period, 31.6% of all patients died (13,079 deaths), including 31.4% of controls (10,573 deaths) and 34.4% of patients with GCA (2506 deaths, $p < 0.001$).

The crude MR (per 1000 PY) for the entire GCA cohort were 40.7 during the first 2 years following the diagnosis, 47.5 at 2–10 years after diagnosis, and 71.1 in the > 10 years of followup. The corresponding rates for controls were 33.57, 43.47, and 60.68, respectively. In most of the study subgroups, MR were higher among patients with GCA than controls and were higher in males (Table 2).

Table 1. Basic characteristics of the study population.

Characteristics	GCA, n = 7294	Controls, n = 33,688	p
Age, yrs, mean ± SD; median	72.4 ± 9.9; 73.16	71.9 ± 9.9; 72.7	< 0.05
Duration of followup, yrs, mean ± SD; median	7.09 ± 4.41; 6.58	7.19 ± 4.5; 6.71	< 0.001
Female sex	5401 (69.1)	23,379 (69.4)	NS
SES[a]			NS
Low	2395 (33.1)	11,091 (33.2)	
Medium	3085 (42.6)	14,357 (42.9)	
High	1755 (24.3)	7986 (23.9)	
Smoker	1801 (24.7)	7253 (21.5)	< 0.001
Diabetes	2154 (29.5)	8798 (26.1)	< 0.001
Hypertension	4626 (63.4)	19,691 (58.5)	< 0.001
Dyslipidemia	4921 (67.5)	20,579 (61.1)	< 0.001

Data are n (%) unless otherwise indicated. [a] Available for 99.2% of data. GCA: giant cell arteritis; NS: not significant; SES: socioeconomic status.

Kaplan-Meier survival analysis. The Kaplan-Meier survival analysis during the entire followup period resulted in significantly shorter survival among patients with GCA than controls in the log-rank test ($p < 0.0001$). Estimated median survival was 13.1 years (95% CI 12.6–13.5) for patients with GCA, compared to 14.4 years (95% CI 14.1–14.6) for controls (Figure 2).

Cox multivariate survival analysis. The Cox multivariate survival analysis demonstrated significantly increased mortality risk among patients with GCA during the first 2 years after the diagnosis (HR 1.14, 95% CI 1.04–1.25) and more than 10 years after diagnosis (HR 1.14, 95% CI 1.02–1.26). The excess risk was highest in patients diagnosed at age 70 years or younger (HR 1.5, 95% CI 1.14–1.99) during the first 2 years, and > 10 years since diagnosis (HR 1.38, 95% CI 1.1–1.7). Male patients demonstrated increased mortality risk during the first 2 years after diagnosis (HR 1.3, 95% CI 1.1–1.5), whereas female patients had an increased mortality risk > 10 years after diagnosis (HR 1.17, 95% CI 1.03–1.32). In the 2- to 10-year followup period, significantly excess risk was observed only in the univariate analysis and was not observed when accounting for the model covariates (Table 3). The covariates of age at diagnosis, smoking, diabetes, and HTN were positively associated with mortality at any followup period and in every subset of subjects (not shown).

DISCUSSION

This large, population-based, retrospective cohort study compared all-cause mortality among GCA patients with age- and sex-matched controls, for a followup period of 16 years. Multivariate analysis found increased risk of mortality among patients with GCA during the first 2 years after diagnosis and again in the period > 10 years after diagnosis. This association was especially prominent in patients who were younger than age 70 at diagnosis.

Table 2. No. deaths and crude mortality rates per 1000 PY among patients with GCA stratified by followup period, age at diagnosis, and sex.

	Followup Period[a], yrs	GCA Deaths	GCA PY	GCA Mortality Rates	Controls Deaths	Controls PY	Controls Mortality Rates
Entire population	0–2	555	13,649	40.66	2136	63,631	33.57
	2–10	1532	32,227	47.54	6635	152,644	43.47
	> 10	419	5891	71.12	1799	29,645	60.68
Males	0–2	232	4130	56.16	783	19,284	40.60
	2–10	517	9041	57.18	2188	42,977	50.91
	> 10	117	1495	78.22	533	7520	70.88
Females	0–2	323	9518	33.99	1353	44,344	30.51
	2–10	1015	23,186	43.78	4447	109,667	40.55
	> 10	302	4395	68.71	1266	22,124	57.22
≤ 70 yrs[b]	0–2	68	5394	12.60	197	26,073	7.56
	2–10	217	14,153	15.33	851	68,700	12.39
	> 10	108	3240	33.33	368	16,386	22.46
> 70 yrs	0–2	487	8254	59	1939	37,558	51.63
	2–10	1315	18,073	72.76	5784	83,944	68.90
	> 10	311	2650	117.33	1431	13,258	107.93

[a]Time since diagnosis/index date. [b]Age at diagnosis/index date. PY: person-years; GCA: giant cell arteritis.

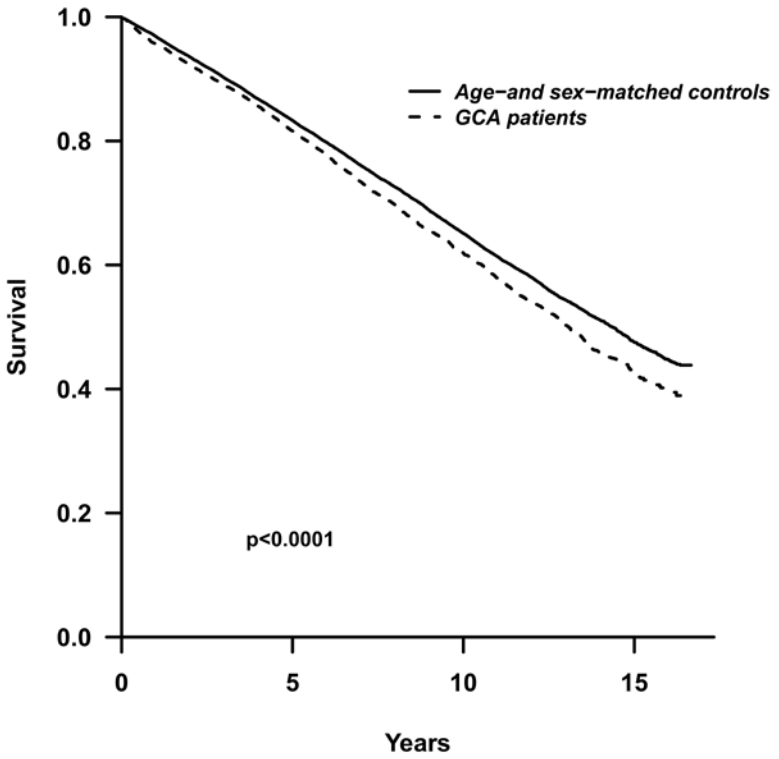

Figure 2. Kaplan-Meier survival curve showing cumulative survival over time in years. GCA: giant cell arteritis.

The reports regarding mortality risk in patients with GCA are contradictory[3,33,35]. A previous metaanalysis that included all the studies addressing GCA mortality published to date found no longterm excess mortality associated with GCA[5]. In addition, that study concluded that the data addressing mortality in the first 2 years following diagnosis and in the late period of the disease are limited. Yet the studies included in that metaanalysis had several methodological flaws. First, most used standardized MR (SMR) as a measure of mortality[7,9,11,13,14,18,19,20]. This method compares observed MR with expected death rates of the general population. Results based on SMR depend on the chosen comparison population[36]. In these studies, patients were obtained either from 1 center or a few tertiary centers and were compared

Table 3. Mortality HR for GCA patients compared with matched controls. All-cause mortality was considered an event. Model was stratified by followup period, age at time of diagnosis, and by sex.

	Followup Period[a], yrs	Univariate Analysis		Multivariate Analysis[b]	
		HR	95% CI	HR	95% CI
Entire population	0–2	1.21	1.10–1.33	1.14	1.04–1.25
	2–10	1.09	1.03–1.16	1.04	0.98–1.10
	> 10	1.17	1.05–1.30	1.14	1.02–1.26
Males	0–2	1.38	1.20–1.60	1.30	1.12–1.50
	2–10	1.12	1.02–1.23	1.06	0.96–1.17
	> 10	1.10	0.90–1.35	1.06	0.86–1.30
Females	0–2	1.11	0.98–1.25	1.05	0.93–1.18
	2–10	1.08	1.01–1.16	1.03	0.96–1.10
	> 10	1.20	1.06–1.36	1.17	1.03–1.32
≤ 70 yrs[c]	0–2	1.66	1.26–2.20	1.50	1.14–1.99
	2–10	1.23	1.06–1.43	1.14	0.98–1.32
	> 10	1.48	1.20–1.84	1.38	1.11–1.71
> 70 yrs	0–2	1.14	1.03–1.26	1.10	0.99–1.21
	2–10	1.06	1.00–1.12	1.02	0.96–1.08
	> 10	1.09	0.96–1.23	1.07	0.95–1.21

[a] Time since diagnosis/index date. [b] The model included these variables: age, sex, dyslipidemia, smoking, hypertension, and diabetes. [c] Age at diagnosis/index date. GCA: giant cell arteritis.

to the general population from the same geographical area. The validity of this type of comparison is questionable, and inferior to using a matched cohort. Second, the populations originated from hospital settings[6,10,12,14,18,19,20] and are more susceptible to referral bias. Last, none of the studies adjusted for CV risk factors, even though CV disease (CVD) is the leading cause of death in patients with GCA.

To our knowledge, Baslund, *et al*[31] conducted the only large population-based study with a matched comparison cohort, which included 1787 patients with GCA from Denmark. Therefore, this is the only study with the validity to be compared to our current study. Baslund, *et al*[31] reported an increased MR ratio in the first 2 years following diagnosis and from 10 years on. Our GCA cohort was similar in terms of age at diagnosis, female ratio, and median followup time[31]. The age of diagnosis distribution was similar to a previous report[37]. Other characteristics, including socioeconomic status, smoking, diabetes, HTN, and dyslipidemia were first considered in our study. The smoking rates in our cohort were similar to those reported in the Israel national survey[38] and the diabetes, HTN, and dyslipidemia rates were compatible with the rates of Western country population in this age group[39,40,41]. The diagnosis age distribution was similar.

We found significant excess short-term mortality in the first 2 years following the diagnosis of GCA, thus supporting many studies including that of Baslund, *et al*[7,10,18,19,31]. Regarding the association between age at GCA diagnosis and mortality, our study was the first to significantly demonstrate increased mortality risk among patients with GCA diagnosed before the age of 70 years, to our knowledge. This finding supports Mohammad, *et al* and Uddhammar, *et al*[7,20], who reported this association, yet failed to achieve statistically significant results owing to the limited number of deaths in this subset. Increased mortality at a younger age of diagnosis was not reported by Baslund, *et al*[31], probably owing to a cutoff age of 75 years and to only a few deaths.

As opposed to most of the studies that found no difference in longterm mortality between patients with GCA and the general population, we found a minor difference in longterm mortality using Kaplan-Meier survival analysis. We assume that this discrepancy most likely arises from differences in study methodology, age composition of cohorts, and duration of followup. Moreover, our results, demonstrating increased mortality during the first 2 years and more than 10 years after diagnosis of GCA and in younger patients, might explain the heterogeneous results regarding GCA mortality to date. Studies with higher proportion of patients younger than 70 years of age at diagnosis or shorter followup times might bias the results toward increased mortality in patients with GCA or vice versa. Thus, because of mortality patterns among patients with GCA, the results regarding longterm mortality are strongly influenced by the study population and design.

GCA is a chronic inflammatory disease, yet flares are most common during the first 2 years after diagnosis[32,33], while large-vessel involvement, including aortic aneurysm and dissection, peaks during the first year following the diagnosis of GCA, and again 10 to 20 years after diagnosis[34]. General CVD is the leading cause of death among patients with GCA and specifically, myocardial infarction (MI) is the first[13,20]. Higher risk for MI and any CVD among patients with GCA was also reported, especially in the first years after diagnosis[42,43,44].

Our study demonstrated a biphasic risk pattern for all-cause mortality, which corresponds with the clinical

course of the disease. The increased mortality risk observed in the early phase (during the first 2 years after diagnosis) may be due to the consequences of vasculitis that lead to inflammatory artery stenosis, organ ischemia, and CVD-associated mortality. The increased mortality risk observed in our study in the late phase (> 10 yrs from diagnosis) may be related to complications of longterm corticosteroid use, which is the treatment of choice, or due to cumulative damage caused by the chronic inflammatory state. Death resulting from aortic aneurysm or dissection may contribute to the excess mortality in both phases.

Our study found an increased mortality risk among males during the first 2 years after diagnosis of GCA, and in females > 10 years after diagnosis. These results imply that males are more susceptible to the early-phase mortality risk factors of the disease, while females are more susceptible to the late-phase mortality risk factors; however, this is a matter for further investigation.

The highest mortality risk observed in our study was found among patients with GCA diagnosed before the age of 70 years. We suggest several possible explanations for this association. The relative effect of GCA-associated mortality is decreased in older age because of the increased cumulative load of traditional risk factors. In addition, because GCA is more prevalent in the older age group, the diagnosis in relatively younger patients is more easily missed and delayed[45], which can promote poor outcomes. In addition, as previously reported, patients diagnosed before the age of 70 years of age tend to have a more aggressive disease, with higher inflammatory response[45], which can increase mortality due to complications of the disease.

Increased mortality risk 2–10 years after diagnosis was observed only in the univariate analysis. Therefore, the increased mortality risk in that period could be attributed to the higher proportion of CV risk factors.

Our study has several strengths. It includes a heterogeneous, nationwide sample representing patients with GCA in Israel. The study used a population-based design with a matched cohort comparison group, thereby avoiding the potential referral bias that often afflicts center-based studies; in addition, the multivariate analysis considered SES and important risk factors. However, there were several limitations, as well. We did not have access to pathology reports and thus we were unable to separate patients diagnosed using a temporal artery biopsy (TAB) from other biopsy-negative patients who were diagnosed based on laboratory, imaging, and clinical findings. Many studies used TAB as their major enrollment criterion[7,17,20,31] and this factor must be taken into consideration when making a comparison. It is important to note that although TAB is the most specific test for diagnosis of GCA, its sensitivity is variable and depends on technical issues[46]. Moreover, TAB is not required for GCA classification, which can be done using the American College of Rheumatology 1990 criteria[47]. Several studies had shown that biopsy-proven patients do not differ regarding disease severity and outcomes from biopsy-negative patients[13,18], including studies conducted in Israel[48]. Nonetheless, the common practice of GCA diagnosis in Israel typically includes a TAB. Therefore, it is reasonable to assume that most of the patients in our GCA cohort were diagnosed using a biopsy.

Another limitation is that because we relied on the CHS database, we were unable to distinguish different clinical variants of GCA, such as frequency of relapses, inflammatory markers, visual impairment, and large-vessel involvement. Information regarding pharmacological treatment administered to patients was lacking as well; thus, we were unable to further explore the separate effect of these variables on MR.

In addition, our study was conducted on the Israeli population. Most of the studies were conducted on Scandinavian populations, which have a higher incidence rate of GCA[7,14,20,31]. When doing such comparison, one must take into consideration the differences in the environment, the genetic background, and the quality of healthcare services. Therefore, any attempt to extrapolate the results to other populations is inherently limited.

Patients with GCA demonstrate excess mortality risk compared with age- and sex-matched controls in the first 2 years after diagnosis, and 10 years and more after diagnosis. The mortality risk was highest in patients diagnosed with GCA before the age of 70 years. These findings have important clinical implications and a careful examination of different treatment strategies according to the interval from diagnosis and to the age of onset may be warranted.

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