Mortality among patients with giant-cell arteritis: A large-scale population-based cohort study

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Running title: Mortality in GCA patients

Abstract

Objectives: 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 gender on the association.

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

Results: The study included 7,294 GCA patients and 34,156 controls. The mean age at start of follow-up was 72.1±9.9 years with 69.2% females. Estimated median survival-time was 13.1 years (95% CI, 12.6-13.5 years) in GCA patients compared with 14.3 years (95% CI, 14.1-14.6) in controls (*P*-value < 0.001).The multivariate analysis demonstrated increased mortality risk in the first 2 years after diagnosis (HR 1.14; 95% CI 1.04-1.2) and >10 years after diagnosis (HR 1.14; 95% CI 1.02-1.3). The mortality-risk was higher in patients diagnosed ≤70 years of age (HR 1.5(95% CI 1.14-1.99) 0-2 years; HR 1.38(95% CI 1.1-1.7) >10 years).

Conclusion: GCA patients have a minor decrease in long-term 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.

Introduction

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

The mortality of GCA patients 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 (7,10,17–19). Increased long-term 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 insulate GCA as the cause for mortality, we used a multivariate model considering socio-demographic variables and cardiovascular risk-factors found to be associated with GCA.

Materials and Methods

Data source

Data were obtained from Clalit Healthcare Services (CHS) comprehensive, electronic database. CHS is the largest health maintenance organization in Israel and serves approximately 4.4 million insured members (over 50% of Israel 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 going a process of diagnosis validation by logistic checks (such as matching the diagnoses from different sources). CHS database was used in several studies before including those addressing GCA patients (21–26), and was demonstrated to have high validity of diagnoses for chronic diseases and for diseases from the rheumatology field (27–30). For this study, the information drawn from the database has been input continuously since computerized systems were first used in CHS, approximately from January 1, 2002, to September 1, 2018 (Fig. 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 one documented diagnosis of GCA (ICD9 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 that 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 that were randomly assigned from the CHS electronic database. Follow-up for GCA patients 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 GCA patient. Follow-up continued until the earliest of the following: death (event) or end of study follow-up on September 1, 2018 (censored cases).

Study variables

For each subject, age, gender and socioeconomic status (SES) at the beginning of follow-up, 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 parameters, 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 (DM), dyslipidemia and smoking prior to index date, were also obtained from the CHS chronic disease registry, which was demonstrated to have 90 to 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 Mann-Whitney U test for continuous variables, and χ^2 test for

categorical variables. Analysis was performed in three different follow-up 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 which occur mainly during the first 2 years after diagnosis (32,33), and large-vessel complications which reaches 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 and were calculated by dividing the number of deaths in a specific stratum with the sum of person-years of that stratum. Survival analysis was performed using Kaplan-Meier method with a post hoc log-rank comparison of GCA patients and controls. The analysis was for the entire follow-period (≈16 years). Death from all-causes was considered as an event and patients who were alive at the end of the study follow-up were considered censored cases.

Multivariate survival analysis was conducted using the Cox proportional hazard model. Death from all-causes was considered an event. Hazard ratios (HR) were calculated comparing GCA and non-GCA subjects. The model accounted for age, gender, smoking, SES, HTN, dyslipidemia and diabetes. We repeated the analysis for the three follow-up periods (0-2 years, 2-10 years and over 10 years) and for different sub-groups based on the age at diagnosis (≤70 years or >70 years) and gender.

Statistical analysis was performed using the Statistical Package for the Social Sciences; SPSS for Windows, V.23.0 (IBM SPSS Statistics), and WINPEPI, (PEPI-for-Windows), computer programs for epidemiologists, V11.65.

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

Results

Cohort characteristics

The study population was comprised of 40,982 subjects, of which 7,294 were GCA patients and 33,886 were age- and sex-matched controls who were not diagnosed with the disease. The mean age of the entire cohort at beginning of follow up was 72.0±9.9 years (median 72.8 years) and 69.3% were women. Among GCA patients, 13.7% (996) were diagnosed at ages 50-59 years, 24.9% (1,816) at ages of 60-69 years, 37.1% (2,706) at ages of 70-79 years and 24.3% (1,776) were diagnosed after the age of 80 years. A minor statistically significant difference in the age of enrollment was observed. It has no clinical significance to our opinion and is attributed to the large-sample size and the fact that the matching was done based on the patients age in years. No statistically significant difference was found in SES between groups. GCA diagnosed patients had a significantly higher prevalence of the traditional cardiovascular risk factors: smoking, diabetes, HTN and dyslipidemia, than controls did (P-value < 0.001) (Table 1).

Mortality rates

During the entire follow-up period, 31.6% of all patients died (13,079 deaths), including 31.4% of controls (10,573 deaths) and 34.4% of GCA patients (2,506 deaths, P-value < 0.001).

The crude mortality rates (per 1,000 person-years) for the entire GCA cohort were 40.7 during the first 2 years following the diagnosis, 47.5 at 2 to 10 years after diagnosis, and 71.1 in the >10 years follow-up period. The corresponding rates for controls were 33.57, 43.47 and 60.68 respectively. In most of the study subgroups, mortality rates were higher among GCA patients than in controls and were higher in males (Table 2).

Kaplan-Meier survival analysis

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

Cox multivariate survival analysis

The Cox multivariate survival analysis demonstrated significantly increased mortality risk among GCA patients 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 HR 1.38 (95% CI 1.1-1.7) > 10 years since diagnosis. 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 2-10 years follow-up 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 hypertension were positively associated with mortality at any follow-up 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 follow-up period of 16 years. Multivariate analysis found increased risk of mortality among GCA patients 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.

The reports regarding mortality risk in GCA patients are contradictory (3,33,35). A recent meta-analysis that included all the studies addressing GCA mortality published to date, found no long-term excess mortality associated with GCA (5). In addition, this 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 this meta-analysis had several methodological flaws: 1) Most used standardized mortality ratios (SMR) as a measure of mortality (7,9,11,13,14,18–20). This method compares observed mortality rates 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 from either one or a few tertiary centers and were compared to the general population from the same geographical area. The validity of this type comparison is questionable, and inferior to using a matched cohort. 2) The populations originated from hospital settings (6,10,12,14,18–20) and are more susceptible to referral bias. 3) None of the studies adjusted for cardiovascular risk factors, which is the leading cause of death in CGA patients.

To our knowledge, Baslund et al. (31), conducted the only large population-based study with a matched comparison cohort, which included 1,787 patients with GCA from Denmark. Therefore, only this is the only study with the validly to be compared to the current study. Baslund et al.(31) reported an increased mortality rate ratio (MRR) 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 follow-up time (31). The age of diagnosis distribution was similar to previous report (37). Other characteristics, including socio-economic status, smoking, diabetes, hypertension 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, hypertension and dyslipidemia rates were compatible with the rates of western country population in this age group (39–41). 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 GCA patients diagnosed before the age of 70 years. This finding supports Uddhamar et al. and Mohammad et al. (7,20), who reported this association, yet failed to achieve statistically significant results due to the limited number of deaths in this subset. Increased mortality at a younger age of diagnosis was not reported by Busland et al., (31) probably due 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 long-term mortality between GCA patients and the general population, we found a minor difference in long-term 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 follow-up. 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 heterogenous results regarding GCA mortality, so far. Studies with higher proportion of patients younger than 70 years of age at diagnosis or shorter follow-up times, might bias the results towards increased mortality in GCA patients or vice-versa. Thus, because of mortality patterns among GCA patients, the results regarding long-term 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 cardiovascular disease (CVD) is the leading cause of death among GCA patients and specifically, myocardial infarction (MI) is the first (13,20). Higher risk for MI and any CVD among GCA patients was also reported, especially in the first years after diagnosis (42–44).

Our study demonstrated a bi-phasic 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 which lead to inflammatory artery stenosis, organ ischemia and CVD associated mortality. The increased mortality risk observed in our study in the late phase (>10 years from diagnosis) may be related to complications of long-term corticosteroid use, which is the treatment of choice, or due to cumulative damage caused by the chronic inflammatory state. Death due to 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 GCA patients diagnosed before the age of 70 years. We suggest several possible explanations for this association. The relative impact of GCA-associated mortality is decreased in older age due to the increased

cumulative load of traditional risk factors. In addition, since 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 cardiovascular risk factors.

Our study has several strengths. It includes a heterogeneous, nationwide sample representing GCA patients 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 socio-economic status 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 that were diagnosed using a temporal-artery biopsy (TAB) from other, biopsy-negative patients, that were diagnosed based on laboratory, imaging and clinical findings. Many studies used TAB as their major enrollment criteria (7,17,20,31) and this factor must be taken into consideration when making a comparison. It is important to note, Although TAB is the most specific test for diagnosis of GCA its sensitivity is variable and depend on technical issues (46). Moreover, TAB is not required in order to classify patients as having GCA, which can be done using The American College of Rheumatology 1990 criteria (47). Several studies had shown that biopsy-proven patients do not differ in terms of 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 due to relying 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 mortality rates.

In addition, our study was conducted on Israeli population. Most of the studies were conducted on Scandinavian population which has 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.

In conclusion, GCA patients 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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Table 1. Basic characteristics of the study population

Characteristic	GCA (n=7,294)	Controls (n=33,688)	Statistical significance (p-value)
Age (mean±SD; median)	72.4±9.9; 73.16	71.9±9.9; 72.7	<0.05
Duration of follow-up, years (mean±SD; median)	7.09±4.41; 6.58	7.19±4.5; 6.71	<0.001
Gender (female; %)	5,401 (69.1%)	23,379 (69.4%)	NS
SES (n; %) [a]			NS
Low	2,395 (33.1%)	11,091 (33.2%)	
Medium	3,085 (42.6%)	14,357 (42.9%)	
High	1,755 (24.3%)	7,986 (23.9%)	
Smoker (n; %)	1,801 (24.7%)	7,253 (21.5%)	<0.001
Diabetes (n; %)	2,154 (29.5%)	8,798 (26.1%)	<0.001
Hypertension (n; %)	4,626 (63.4%)	19,691 (58.5%)	<0.001
Dyslipidemia (n; %)	4,921(67.5%)	20,579 (61.1%)	<0.001

CI, confidence-interval; GCA, giant-cell arteritis; NS, not significant; SD, standard-deviation; SES, socio-economic status;

[a] Available for 99.2% of data.

Table 2. Number of deaths and crude mortality rates per 1000 person-years among GCA patients stratified by follow-up period, age at diagnosis and gender

		GCA			Controls		
	Follow-up period[a]	Deaths	Person years	Mortality rates	Deaths	Person years	Mortality rates
Entire population	**0-2 years**	555	13,649	40.66	2,136	63,631	33.57
	2-10 years	1,532	32,227	47.54	6,635	152,644	43.47
	>10 years	419	5,891	71.12	1799	29,645	60.68
Males	**0-2 years**	232	4,130	56.16	783	19,284	40.60
	2-10 years	517	9,041	57.18	2,188	42,977	50.91
	>10 years	117	1,495	78.22	533	7,520	70.88
Females	**0-2 years**	323	9,518	33.99	1,353	44,344	30.51
	2-10 years	1,015	23,186	43.78	4,447	109,667	40.55
	>10 years	302	4,395	68.71	1,266	22,124	57.22
≤70 years[b]	**0-2 years**	68	5,394	12.60	197	26,073	7.56
	2-10 years	217	14,153	15.33	851	68,700	12.39
	>10 years	108	3,240	33.33	368	16,386	22.46
>70 years	**0-2 years**	487	8,254	59	1,939	37,558	51.63
	2-10 years	1,315	18,073	72.76	5,784	83,944	68.90
	>10 years	311	2,650	117.33	1,431	13,258	107.93

CI, confidence-interval; GCA, giant-cell arteritis;

[a] Time since diagnosis/index date; [b] age at diagnosis/index date

Table 3. Mortality hazard ratios (HRs) for GCA patients compared with matched controls. All-cause mortality was considered an event. Model was stratified by follow-up period, age at time of diagnosis and by gender

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

CI, confidence-interval; HR, hazard ratio;

[a] Time since diagnosis/index date [b] The model included the variables: age, gender, dyslipidemia, smoking, hypertension and diabetes [c] Age at diagnosis/index date

Fig. 1 Study population

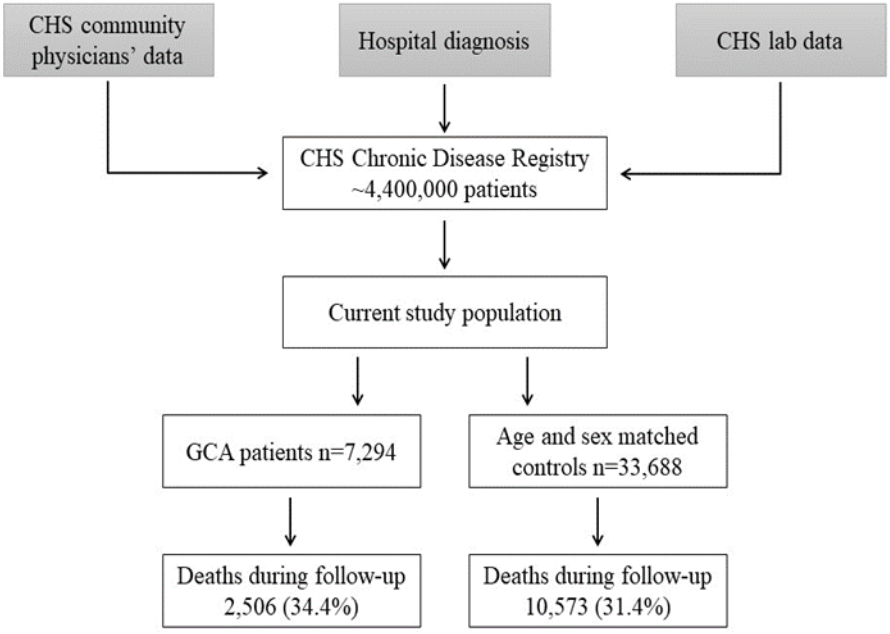

Fig. 2 Kaplan-Meyer survival curve showing cumulative survival over time in years