Characteristics and Long-Term Prognosis of Holocaust Survivors Presenting with Acute Myocardial Infarction

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ABSTRACT: **Background:** Catastrophic life events are associated with the occurrence of cardiovascular incidents and worsening of the clinical course following such events.

Objectives: To evaluate the characteristics and long-term prognosis of Holocaust survivors presenting with acute myocardial infarction (AMI) compared to non-Holocaust survivors.

Methods: Israeli Jews who were born before 1941 and had been admitted to a tertiary medical center due to AMI during the period 2002–2012 were studied. Holocaust survivors were compared with non-Holocaust survivor controls using individual age matching.

Results: Overall 305 age-matched pairs were followed for up to 10 years after AMI. We found a higher prevalence of depression (5.9% vs. 3.3%, $P = 0.045$) yet a similar rate of cardiovascular risk factors, non-cardiovascular co-morbidity, severity of coronary artery disease, and in-hospital complications in survivors compared to controls. Throughout the follow-up period, similar mortality rates (62.95% vs. 63.9%, $P = 0.801$) and reduced cumulative mortality (0.9 vs. 0.96, HR = 0.780, 95%CI 0.636–0.956, $P = 0.016$) were found among survivors compared to age-matched controls, respectively. However, in a multivariate analysis survival was not found to be an independent predictor of mortality, although some tendency towards reduced mortality was seen (AdjHR = 0.84, 95%CI 0.68–1.03, $P = 0.094$). Depression disorder was associated with a 77.9% increase in the risk for mortality.

Conclusions: Holocaust survivors presenting with AMI were older and had a higher prevalence of depression than controls. No excessive, and possibly even mildly improved, risk of mortality was observed in survivors compared with controls presenting with AMI. Possibly, specific traits that are associated with surviving catastrophic events counter the excess risk of such events following AMI.

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KEY WORDS: prognosis, genocide/Holocaust, coronary artery disease (CAD), acute myocardial infarction (AMI)

The long-term impact of catastrophic experience in general and genocidal experiences specifically that occur early in life on mental and physical health is the subject of much interest and research [1-3]. Acute life "stressors" such as bereavement [4], particularly catastrophic events such as earthquakes or terrorist attacks, have been associated with coronary heart disease events [4-7], especially acute myocardial infarction (AMI) [8]. Furthermore, psychosocial factors that could result from such events could contribute to worsening of the clinical course and prognosis in patients with coronary heart disease (CAD) [9].

Throughout the World War II Holocaust (1939–1945) millions of Jews in Europe were expelled from their homes/countries, separated from their families, sent to ghettos or concentration camps, or exterminated. Hence, survivors of the Holocaust who are alive today constitute a group of aging people who experienced extreme catastrophic stress and trauma of a physical and mental nature as young people more than 70 years ago. The immediate and short to medium-term health effects, mostly mental consequences, have been well documented [1,10,11]. However, the results of studies linking Holocaust traumatic stress to morbidity risk, cardiovascular morbidity and death are inconclusive or even contradicting [1,3,10-14], with most studies being community-based, and centered on small samples, self-report data, or records obtained from clinics. Moreover, data evaluating AMI in Holocaust survivors are extremely sparse.

In this paper we report the first study evaluating the characteristics and long-term prognosis of Holocaust survivors presenting with AMI compared to age-matched controls without such a background.

PATIENTS AND METHODS

This retrospective observational study included patients who had been admitted to a tertiary medical center for AMI during the period 2002–2012. Inclusion criteria were Israeli Jews born before 1941 with a status of Holocaust survival (yes or no) recorded in the computerized systems. Holocaust survival status classification is the result of a preliminary computerized

screening based on demographic characteristics at admission (e.g., year and country of birth and immigration to Israel) that defines whether the patient could potentially be a Holocaust survivor. After the latter computerized screening each patient was interviewed by an authorized social worker responsible for assistance in filing for further social assistance to which Holocaust survivors are entitled.

DATA SOURCES AND CLASSIFICATIONS

Data were obtained from the hospital's computerized information systems. The data included demographic and clinical characteristics, cardiovascular risk factors and co-morbidities, interventions administered for the AMI, and clinical workup (blood tests, echocardiography, coronary angiography). Mortality data were obtained from the hospital's mortality database, updated weekly by the Ministry of the Interior Population Registry.

AMI diagnosis was identified based on the international Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes: ST-elevation AMI (STEMI) 410.0*–410.6* and Non-ST-elevation AMI (NSTEMI) 410.7*–410.9*. The results of laboratory tests were divided into three categories (below normal level, within the normal range, and above normal level) according to the appraisals of the testing laboratory. Grouping of diseases and interventions were based on ICD-9-CM discharge codes as previously described [15-17].

STUDY GROUPS

In the primary analysis all recorded Holocaust survivors and non-Holocaust survivors were compared. Thereafter, individual age matching was performed; for every Holocaust survivor a subject with minimal age difference from the control group was matched.

OUTCOMES

The primary outcome was all-cause mortality up to 10 years following admission with acute myocardial infarction.

STATISTICAL ANALYSIS

Statistical analysis was performed using IBM SPSS Statistics 22 software. Patient characteristics were presented as mean and standard deviation (SD) (for continuous variables) and n and percent for the categorical data, and were compared using Student's *t*-test (Mann-Whitney test for non-symmetric distributions) and chi-square test (Fisher exact test for "small cells") respectively. A comparison of length of follow-up between the groups was performed using the independent-samples median test. Cumulative mortality and survival were compared between the study groups using survival approach: log rank (Kaplan-Meier) test and Cox proportional hazards regression. In addition, a Cox proportional multivariate model was built in which the patients' baseline characteristics significantly related to the outcome. For each test, $P < 0.05$ was considered statistically significant.

RESULTS

Overall 1262 patients were detected: 305 Holocaust survivors and 957 controls. The results of primary analysis showed that survivors were significantly older (approximately 4 years) than controls (82.96 ± 6.71 vs. 78.91 ± 6.83, $P < 0.001$). More specifically, 210 of the 305 survivors (68.9%) were 80 years old or older, compared to only 401/957 (41.9%) in the control group ($P < 0.001$). Compared with the controls, survivors had an increased rate of chronic renal failure (187 vs. 497, 61.3% vs. 51.9%, $P = 0.004$), while history of smoking (20 vs. 136, 6.6% vs. 14.2%, $P < 0.001$) and chronic obstructive pulmonary disease (COPD) (15 vs. 94, 4.9% vs. 9.8%, $P = 0.008$) were less frequent. Depression disorder was more prevalent among survivors (18 vs. 32, 5.9% vs. 3.3%, $P = 0.046$). Diagnostic coronary angiography (117 vs. 522, 38.4% vs. 54.5%, $P < 0.001$) as well as interventional treatments: percutaneous coronary intervention (PCI) (106 vs. 435, 34.8% vs. 45.5%) or coronary artery bypass graft (CABG) (15 vs. 105, 4.9% vs. 11.0%, $P < 0.001$) were performed less frequently in survivors.

Mortality rates throughout the follow-up period up to 10 years were 62.95% (cumulative mortality 0.900) in survivors and 50.99% (cumulative mortality 0.822) in controls respectively: hazard ratio (HR) 1.266, 95% confidence interval (95%CI) 1.071–1.496, $P = 0.006$. However, following age adjustment no statistically significant difference was found in the risk for mortality between survivors and controls (AdjHR = 0.972, 95%CI 0.819–1.153, $P = 0.972$).

AGE-MATCHED ANALYSIS

Individual age matching between survivors and controls was performed due to significant disparities in age distribution between the groups, as mentioned. A total of 610 participants were included: 305 survivors and 305 age-matched controls. Baseline characteristics and comparison between survivors and age-matched controls are presented in Table 1. More survivors were born in Europe/Former Soviet Union and immigrated to Israel at an older age (i.e., after the Holocaust) as compared to controls. As in the non-age-matched analysis, smoking and COPD were more prevalent among controls than among survivors, whereas depression disorder was significantly more prevalent among survivors compared with controls. No differences in the rate of diagnostic coronary angiography or interventional treatments (PCI or CABG) were found between the groups.

The follow-up periods lasted up to 3652 days in the survivor group (median 1026 days) and up to 3485 days in the age-matched control group (median 913 days) with no significant difference between the groups ($P = 0.105$). Throughout the follow-up period, mortality rates among survivors and age-matched controls were 62.95% and 63.9% respectively ($P = 0.801$). However, reduced cumulative mortality was noted among survivors (0.900) compared with age-matched con-

Table 1. Baseline characteristics: comparison between Holocaust survivors versus age-matched non-Holocaust survivors

Demographics	Holocaust survivors*		Total (n=610)	*P*
	No (n=305)	Yes (n=305)		
Age, years, mean (SD)	82.97 (6.74)	82.96 (6.71)	82.96 (6.72)	0.986
Gender: Male	158 (51.8)	151 (49.5)	309 (50.7)	0.571
Region of birth				
Former Soviet Union	123 (40.3)	229 (75.1)	352 (57.7)	< 0.001
Israel	12 (3.9)	0 (0)	12 (2.0)	
Asia	17 (5.6)	0 (0)	17 (2.8)	
Europe	21 (6.9)	42 (13.8)	63 (10.3)	
Africa	85 (27.9)	20 (6.6)	105 (17.2)	
Middle East	33 (10.8)	14 (4.6)	47 (7.7)	
America/Other	14 (4.6)	0 (0)	14 (2.3)	
Immigration age, mean (SD)	44.41 (20.85)	52.52 (20.79)	48.56 (21.19)	< 0.001
Family status				
Single	3 (1.0)	6 (2.0)	9 (1.5)	
Married	189 (62.0)	170 (55.7)	359 (58.9)	
Divorced	13 (4.3)	15 (4.9)	28 (4.6)	0.256
Widower	47 (15.4)	42 (13.8)	89 (14.6)	
Other/Unknown	53 (7.4)	72 (23.6)	125 (20.5)	
Residency: Rural	25 (8.4)	27 (8.9)	52 (8.7)	0.859
Cardiac diseases				
Cardiomegaly	31 (10.2)	25 (8.2)	56 (9.2)	0.400
Supraventricular arrhythmias	95 (31.1)	89 (29.2)	184 (30.2)	0.597
Congestive heart failure	85 (27.9)	87 (28.5)	172 (28.2)	0.857
Pulmonary heart disease	49 (16.1)	42 (13.8)	91 (14.9)	0.426
Chronic ischemic heart disease	183 (60.0)	193 (63.3)	376 (61.6)	0.405
Prior AMI	40 (13.1)	48 (15.7)	88 (14.4)	0.357
Atrioventricular block	20 (6.6)	22 (7.2)	42 (6.9)	0.749
Cardiovascular risk factors				
Renal diseases	172 (56.4)	187 (61.3)	359 (58.9)	0.217
Diabetes mellitus	128 (42.0)	130 (42.6)	258 (42.3)	0.870
Dyslipidemia	193 (63.3)	203 (66.6)	396 (64.9)	0.396
Hypertension	184 (60.3)	192 (63.0)	376 (61.6)	0.505
Obesity	33 (10.8)	45 (14.8)	78 (12.8)	0.146
Smoking	35 (11.5)	20 (6.6)	55 (9.0)	0.034
Peripheral vascular disease	41 (13.4)	52 (17.0)	93 (15.2)	0.215
Other disorders				
Chronic obstructive pulmonary disease	37 (12.1)	15 (4.9)	52 (8.5)	0.001
Neurological disorders	104 (34.1)	106 (34.8)	210 (34.4)	0.865
Malignancy	26 (8.5)	23 (7.5)	49 (8.0)	0.655
Anemia	235 (77.0)	218 (71.5)	453 (74.3)	0.115
Schizophrenia/Psychosis	11 (3.6)	7 (2.3)	18 (3.0)	0.339
Anxiety/Panic disorders	2 (0.7)	5 (1.6)	7 (1.1)	0.450
Depression disorder	8 (2.6)	18 (5.9)	26 (4.3)	0.045
Alcohol/drug addiction	3 (1.0)	2 (0.7)	5 (0.8)	1.000
Administrative data of hospitalization				
Admitted/transposed to ICCU	98 (32.1)	113 (37)	211 (34.6)	0.202
Total hospital duration (days)				
Mean (SD)	10.90 (9.47)	11.01 (9.74)	10.95 (9.60)	0.546
> 7 days	177 (58.0)	184 (60.3)	361 (59.2)	0.564
Clinical characteristics of hospitalization				
ST-elevation myocardial infarction	70 (23.0)	72 (23.6)	142 (23.3)	0.848
In-hospital complications				
Ventricular tachycardia/ fibrillation	7 (2.3)	8 (2.6)	15 (2.5)	0.794
Ischemic/hemorrhagic stroke	9 (3.0)	7 (2.3)	6 (2.6)	0.612
Acute respiratory failure	8 (2.6)	12 (3.9)	20 (3.3)	0.363
Shock	4 (1.3)	5 (1.6)	9 (1.5)	0.737
Bleeding	17 (5.6)	14 (4.6)	31 (5.1)	0.580
Sepsis/septicemia	18 (5.9)	18 (5.9)	36 (5.9)	1.000
Hyperkalemia	81 (25.6)	72 (23.6)	153 (25.1)	0.87
Hyponatremia	59 (19.3)	65 (21.3)	124 (20.3)	0.546
Results of echocardiography				
Performance of echocardiography	176 (57.7)	177 (58)	353 (57.94)	0.935
Severe LV dysfunction	29 (16.5)	23 (13)	52 (14.7)	0.356
LV hypertrophy	11 (6.3)	14 (7.9)	25 (7.1)	0.543
Mitral regurgitation	19 (10.8)	26 (14.7)	457 (12.7)	0.273
Pulmonary hypertension	35 (19.9)	34 (19.2)	69 (19.5)	0.873
Results of angiography				
Performance of coronary angiography	115 (37.7)	117 (38.4)	232 (38.0)	0.868
Severity of CAD				
No or non-significant	10 (8.7)	9 (7.8)	19 (8.2)	0.703
One vessel	20 (17.4)	23 (19.8)	43 (18.6)	
Two vessels	21 (18.3)	27 (23.3)	48 (20.8)	
Three vessels/LMCA	64 (55.7)	57 (49.1)	121 (52.4)	
Type of treatment				
Non-invasive	182 (59.7)	184 (60.3)	366 (0.0)	0.779
Percutaneous coronary intervention	104 (34.1)	106 (34.8)	210 (34.4)	
Coronary artery bypass graft	19 (6.2)	15 (4.9)	34 (5.6)	

*Data presented as the number of patients and percent of categories unless otherwise specified

SD = standard deviation, LV = left ventricular, LMCA = left main coronary artery, CAD = coronary artery disease, ICCU = intensive cardiac care unit

trols (0.956) (HR = 0.780, 95%CI 0.636–0.956, *P* = 0.016). Survival following AMI in both groups is presented in a Kaplan-Meier curve in Figure 1.

The results of a multivariate prognostic model for mortality following AMI is shown in Table 2. After adjustment for the investigated potential confounders, survival was not found to be a statistically significant independent predictor of mortality, However, a tendency towards reduced risk for mortality (19.2% decrease) among survivor AMI patients was found (*P* = 0.094). Interestingly, the existence of depression disorder was associated with a 77.9% increase in mortality during the follow-up period.

DISCUSSION

To the best of our knowledge the current study evaluated, for the first time, the characteristics and long-term prognosis of Holocaust survivors presenting with AMI compared to controls without this exposure. The main findings of this study were that except for being significantly older and having a

Figure 1. Kaplan-Meier Survival curve following AMI: Holocaust survivors vs. age-matched non-Holocaust survivors

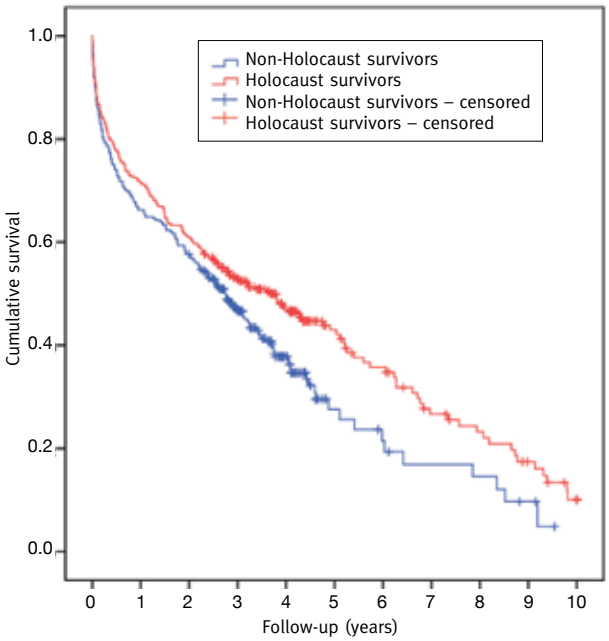

Table 2. Multivariate analysis for prediction of mortality following AMI among Holocaust survivors and age-matched non-Holocaust survivors

Variable/Values		AdjHR	95%CI		*P*
Recorded Holocaust survivor	Yes vs. no	0.839	0.682	1.031	0.094
Demographics					
Age	One year increase	1.059	1.041	1.077	< 0.001
Co-morbidities					
Neurological disorders		1.806	1.467	2.223	< 0.001
Malignancy		2.212	1.550	3.156	< 0.001
Anemia		1.417	1.100	1.825	0.007
Depression disorder		1.779	1.114	2.839	0.016
In-hospital complications					
Hyperkalemia		1.500	1.196	1.880	< 0.001
Sepsis/septicemia		3.185	2.142	4.735	< 0.001
Type of treatment	Non-invasive vs. invasive (PCI or CABG)	1.986	1.555	2.537	< 0.001

AdjHR = adjusted hazard ratio, CI = confidence interval, PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft

higher prevalence of depression disorder, Holocaust survivors were very similar to non-Holocaust survivor controls with almost no significant changes in the prevalence of cardiovascular risk factors, non-cardiovascular co-morbidity, in-hospital complications, hospitalization duration, or coronary angiography findings. Throughout the follow-up period while similar mortality rates were observed in both groups, cumulative mortality was significantly lower among survivors compared with age-matched controls. Nevertheless, in a multivariate analysis survival was not found to be an independent predictor of mortality, although some tendency towards reduced mortality was seen ($P = 0.094$). Depression disorder, which is much more common among survivors [2], was associated with an increased risk of 78% for mortality following AMI.

In an earlier study Eitenger [11] reported 18% higher mortality among Holocaust camp survivors in the 20 years after the end of the Second World War; however, this excess in mortality was due mainly to infectious diseases, suicide and "unknown" rather than coronary artery disease. In the later Israel Ischemic Heart Disease study, which followed 10,059 Jewish male government and municipal male employees from 1963 to 1986, Williams et al. [1] showed that Holocaust survivors had similar mortality rates to those of non-Holocaust survivors (males) 20–34 years after exposure, with no changes in the cause of death between the groups. Extending the latter findings to women and for a longer period, Collins et al. [10] found that all-cause or cardiovascular mortality rates among the Holocaust survivors were not higher than in the control group and even tended to be somewhat lower. The authors concluded that similar mortality rates in both groups could be explained by the exceptionally resilient adaptation qualities of the long-term Holocaust survivors.

In a very different context, a 10 year mortality study (1983–93) of men and women living in Beirut during the civil war showed an association confined to women with high cardiovascular mortality who had been exposed to traumatic circumstances [14].

A recent meta-analysis exploring the association of war-related stress (both in the military and the civilian setting) and all-cause mortality included 30 publications, 220 risk estimates and over 9 million persons (including Holocaust survivors). After adjustment for multiple covariates, the risk of death was not different between those who experienced war-related stress and those who did not [3]. Sagi-Schwarz et al. [12] recently reported a large retrospective population-based cohort study examining age of death among Holocaust survivors compared to peers without a Holocaust background. Although the cause of death was not analyzed the authors found that the risk to die younger was significantly lower among Holocaust survivors than those without a Holocaust background.

Several reasons could be suggested to explain the results of the current study and those of others that did not find excess mortality, or even found a tendency towards improved outcomes in Holocaust survivors in general and those with AMI specifically. First, the findings may be influenced by a differential mortality or selection effect, i.e., survival following confinement in a Nazi concentration camp during the Holocaust or in a prisoner of war camp is related to a specific genetic, temperamental, physical, or psychological make-up that enabled them to survive

during the Holocaust [12,18-20] and predisposed them to reach a relatively old age. Hence, this attribute may have countered the deleterious effects of stress on morbidity and mortality. The latter explanation is supported by our finding that Holocaust survivors, despite being significantly older than the controls, had no significant excess in cardiovascular risk factors and non-cardiovascular co-morbidity. Furthermore, despite a higher prevalence of depression disorder that is associated with worse outcomes following AMI in the current study and consistently in previous reports [21,22], and lower rates of interventional treatments (non-age-matched) that often improve prognosis [23], no excess in age-adjusted mortality was found. Second, exposure of a person to such harrowing experiences could result in him/her being less susceptible and more competent to deal with future stressful events (e.g., AMI) both physically and mentally [3,24].

LIMITATIONS

One limitation is the inclusion of patients from one region of the country, and despite being the largest it might not represent national coverage. Second is the absence of mortality causes and additional outcomes. Third, we used a retrospective methodology with reliance on treating physicians' diagnoses and routinely collected data, hence other potentially uncontrolled confounders might have existed. Fourth, additional details further characterizing the depressive disorder of the patients in the current study were not available (e.g., need for psychiatric referral, prescription of antidepressant drugs, or some other measure of mental response to the event). The final limitation is a potential recording bias for Holocaust survival, although this became routine and mandatory throughout the study period.

CONCLUSIONS

Holocaust survivors presenting with AMI were found to have a higher prevalence of depression disorder but were otherwise similar to age-matched controls. A reduced cumulative mortality throughout the follow-up period was found among survivors versus age-matched controls. However, survival was not found to be an independent predictor of mortality in a multivariate analysis, although a non-significant tendency towards reduced mortality was seen. Interestingly, depression disorder was associated with a 77.9% increase in the risk for mortality. Additional studies more extensively exploring the balance between the risk for worse outcomes following AMI in subjects with past genocidal exposures and potential countering traits of survivors are warranted.

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