Usefulness of Malignancy as a Predictor of Worse In-Hospital Outcomes in Patients With Takotsubo Cardiomyopathy

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Takotsubo cardiomyopathy (TC) is a form of dilated cardiomyopathy often associated with physical or emotional stress. Association with cancer has been reported, however, in-hospital outcomes in TC patients with history of malignancy have not been fully characterized. We conducted a retrospective chart review of hospitalized patients with diagnosis of TC between January 2006 and January 2017. Patients were divided into 2 groups based on the previous history of malignancy. Presenting symptoms, cardiac imaging and short-term events including in-hospital complications and mortality, were compared. Of 318 patients with TC, 81 (25.4%) had a previous diagnosis of cancer. Mean age was 67.5 (SD 12.6), 151 (47.5%) were African American, 122 (38.4%) Caucasian, and 10 (3.1%) of other ethnicities. Patients with history of malignancy were older (70.0 [SD 10.6] vs 66.6 [SD 13.1] years, p = 0.03), had higher heart rate on presentation (93 [SD 19] vs 87 [SD 25] beats/minute, p = 0.03), higher prevalence of severely decreased cardiac function (left ventricular ejection fraction <25%) (29.6% vs 16%, p = 0.01), longer hospitalization (7 (4−13) vs 4 (3-8) days, p = 0.001) and experienced more in-hospital cardiac arrests (6 [7.4%] vs 5 [2.1%], p = 0.035) compared with patients without malignancy history. Higher percentage of longer hospitalization and left ventricular ejection fraction <25% in the cancer group persisted after controlling for sepsis, chemotherapy exposure, and metastatic disease. In conclusion, in a racially diverse hospitalized population of TC, prevalence of cancer history is high, and diagnosis of previous malignancy is associated with adverse in-hospital outcomes. **(Am J Cardiol 2019;123:995−1001)**

Stress-induced or takotsubo cardiomyopathy (TC) is a syndrome characterized by transient impairment of left ventricular (LV) function with characteristic wall motion abnormalities (WMA) unexplained by coronary artery disease (CAD) on coronary angiography.[1,2] The pathogenesis of TC remains uncertain, but recent exposure to psychological or physical stress can be elicited in most cases, suggesting that catecholamine excess may play a mechanistic role.[1] Several studies have showed a higher prevalence of malignancies in TC patients compared with the general population.[3−6] Cancer patients are often under heavy physical and emotional stress from surgery, chemotherapy, fear, and anxiety[7] and it has been hypothesized that prolonged exposure to stress hormones might contribute to their increased risk of TC. In recent studies, history of malignancy was reported to be an independent predictor of adverse cardiovascular outcomes in predominantly Caucasian population.[4−6] The effect of malignancy diagnosis on in-hospital TC outcomes and the association of African American (AA) race have not been examined despite recent literature suggesting possible racial and ethnic differences.[8,9] Therefore, this investigation studied racially diverse, inner city population of the United States to estimate prevalence of malignancy in patients admitted with TC, and the effects of cancer diagnosis on in-hospital outcomes.

Methods

This was a single-center, retrospective study of consecutive patients admitted to Medstar Washington Hospital Center in Washington, DC from January 2006 to January 2017. Electronic medical records were queried for patients over the age of 18 with a diagnosis of TC. International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification (ICD-9-10-CM) codes for TC or stress-induced cardiomyopathy were used for the search. Chart reviews of the identified patients were conducted and those who met the Modified Mayo Clinic Criteria of diagnosis[10] (Figure 1) were included. All patients underwent coronary angiography for assessment of CAD. Obstructive CAD was defined as the presence of a coronary epicardial vessel with ≥50% stenosis.[11] Patients with obstructive CAD were included if WMA were not in the distribution of the CAD. This is based on the observation that up to 15% of patients in TC registries had concomitant CAD.[1] All angiograms, echocardiograms, and electrocardiograms (ECGs) were read by board-certified cardiologists.

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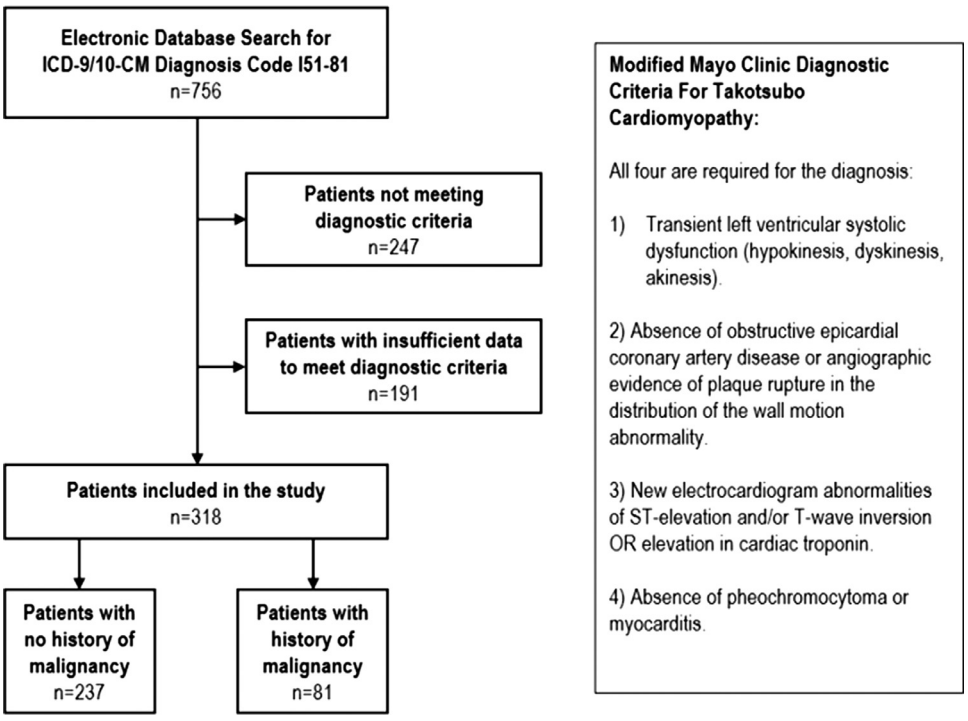

Figure 1. Patient selection and diagnostic criteria
ICD-9/10-CM: International Classification of Disease, Ninth and Tenth Revision Clinical Modification Code.

Patients were divided in 2 groups based on the presence of history of malignancy before and/or during the hospitalization for TC. Malignancy was defined by the documented solid or hematologic cancer or melanoma regardless of the time of diagnosis and current activity. Nonmelanoma skin cancers were excluded. Baseline characteristics, presenting vital signs, symptoms, ECG changes, laboratory findings, echocardiograms, coronary angiograms, and in-hospital outcomes were collected. Patients with malignancy were stratified based on the type of cancer, history of chemotherapy or metastasis before the TC event. Chemotherapy use was defined as any previous chemotherapy regimen regardless of the timing, duration or type. Metastatic disease was defined as any documented evidence of metastases regardless of the timing or extent. Sepsis was defined as the presence of systemic inflammatory response syndrome[12] along with the presence of an infective source or the isolation of infective organisms from body fluids. Standard 12-lead ECGs were used to assess ST-segment and T-wave changes. ST segment elevation and T-wave inversion were defined by the published criteria.[13] Baseline transthoracic echocardiograms were used to assess the severity of LV impairment and the distribution of WMA if they were obtained within 2 days of the TC diagnosis. In patients with unavailable baseline echocardiograms LV angiograms were used for LV ejection fraction (LVEF) assessment. LV impairment was categorized as mild (LVEF >40%), moderate (LVEF 25%−39%), and severe (LVEF <25%) and WMA distribution as apical, midventricular, basal and combined in patients who had any combination of regional WMA. Recovery of LV function was assessed by the first repeated echocardiogram within 3 months of the TC event and defined as improvement of LVEF to 55% or above.

Continuous variables are reported as means and standard deviation or as medians and interquartile range (IQR) depending on data normality. Categorical variables are reported as frequencies and percentages. Comparisons were conducted using *t* test/analysis of variance for continuous variables with normal distribution and Wilcoxon rank sum test/Krusal Wallis test for continuous variables not normally distributed. Categorical variables were compared using Chi-square test or Fisher's exact, as appropriate. Stratified analysis was conducted to explore effect of ethnicity within malignancy and nonmalignancy groups. Regression analysis was used to study the interaction effect between ethnicity and malignancy. Regression analysis was performed on log transformed hospital length of stay and on cube root transformed intensive unit care (ICU) length of stay to reduce skew in the data. Logistic regression was used for the categorical variables. SAS version 9.4 software was used for data analysis, p value <0.05 (2-tailed) was considered to be statistically significant. The Medstar Health Research Institute's Investigational Review Board approved the study protocol.

Results

The study flow is shown in Figure 1 and the distribution of patients based on cancer type, chemotherapy use and presence of metastatic disease in Supplementary Figure 1. No patient received chemotherapy during hospitalization for the TC event. Baseline characteristics, past medical history and the initial ECG are shown in Table 1. Patients in the malignancy group were older and had faster heart rate on presentation than those in the nonmalignancy group. No significant differences were observed in gender,

Table 1
Anthropometric and clinical characteristics

Variable	All patients (n = 318)	Malignancy		p Value
		No (n = 237)	Yes (n = 81)	
Age (years)	67.5 (12.6)	66.6 (13.1)	70.0 (10.6)	0.03
Women	280 (88%)	211 (89%)	69 (85%)	0.47
Men	38 (12%)	26 (11%)	12 (15%)	
White	122 (38%)	89 (38%)	33 (41%)	0.08
Black	151 (48%)	108 (46%)	43 (53%)	
Unknown	35 (11%)	30 (12%)	5 (6%)	
Other	10 (3%)	10 (4%)	0 (0%)	
Hypertension	249 (78%)	185 (78%)	64 (79%)	0.98
Diabetes mellitus	78 (25%)	56 (24%)	22 (27%)	0.63
Chronic obstructive pulmonary disease	57 (18%)	47 (20%)	10 (12%)	0.18
Atrial fibrillation	40 (13%)	27 (11%)	13 (16%)	0.37
Coronary artery disease*	44 (14%)	35 (15%)	9 (11%)	0.52
Chronic kidney disease	26 (8%)	17 (7%)	9 (11%)	0.38
Smoking	136 (43%)	102 (43%)	34 (42%)	0.97
Alcoholism	25 (8%)	17 (7%)	8 (10%)	0.59
Chest pain	173 (54%)	136 (57%)	37 (46%)	0.09
Shortness of breath	139 (44%)	103 (44%)	36 (44%)	0.98
Syncope	22 (7%)	18 (8%)	4 (5%)	0.58
Cardiac arrest	14 (4%)	10 (4%)	4 (5%)	0.76
Gastrointestinal symptoms	39 (12%)	31 (13%)	8 (10%)	0.57
Systolic blood pressure (mm Hg)	124 (27)	124 (27)	123 (29)	0.69
Diastolic blood pressure (mm Hg)	73 (17)	73 (17)	72 (17)	0.55
Heart rate (beats/minute)	88 (21)	87 (19)	93 (25)	0.03
White Blood Cells (cells/μl)	11118 (5265)	10791 (5388)	12063 (4801)	0.06
Hemoglokin (gm/dl)	11.6 (2)	11.7 (2)	11.3 (2)	0.07
Troponin-I (ng/ml)	7.2 (16.8)	7.3 (17.4)	6.7 (15.2)	0.78
Creatine kinase-MB (ng/ml)	16.7 (33.7)	18.1 (37.7)	12.8 (16.6)	0.30
Creatinine (mg/dl)	1.2 (1.2)	1.1 (1.2)	1.3 (1.1)	0.23
Electrocardiogram changes				
ST segment elevation	101 (33%)	71 (31%)	30 (38%)	0.3
T-wave inversion	187 (60%)	143 (62%)	44 (56%)	0.4
Home medications				
Aspirin	141 (53%)	98 (50%)	43 (61%)	0.12
Angiotensin converting enzyme inhibitors/angiotensin receptor blockers	123 (46%)	90 (46%)	33 (47%)	0.94
Beta blockers	131 (49%)	92 (47%)	39 (56%)	0.25
Anticoagulants	38 (14%)	25 (13%)	13 (18%)	0.32

Data are expressed as number (percentage) or as mean (standard deviation).
* CAD defined as less than 50% reduction in the luminal diameter of a major epicardial artery.

ethnicity, medical or social history, cardiac medication use, symptoms, blood pressure or laboratory values on presentation.

Table 2 shows in-hospital outcomes. Patients in the malignancy group suffered more cardiac arrests and had longer hospitalizations compared with those in the nonmalignancy group. Other in-hospital complications/outcomes were not significantly different between the groups. The analysis of baseline cardiac imaging characteristics (Table 3) showed higher prevalence of severe LV impairment on presentation in patients with malignancy compared with those without. Apical WMA was the most common phenotype and there was no significant difference in the WMA pattern between groups. A follow-up echocardiogram was documented within 3 months in 138 patients (43.4% of the study sample). Average time to follow-up echocardiogram was similar between groups with no significant difference in the percentage of recovery of LV function; however, there was an overall trend for reduced recovery in patients with more severe LV impairment on presentation (Table 3).

To exclude confounding effects of sepsis that patients with malignancy may be more prone to, we conducted a separate analysis after excluding patients with diagnosis of sepsis during the incident TC hospitalization (n = 25). In the remaining cohort (n = 293), there was no significant difference in the presenting heart rate and in-hospital cardiac arrests (86 [SD 19] vs 90 [SD 25] beats/minute, p = 0.17) and (5 [2.2%] vs 3 [4.3%] arrests, p = 0.40) between the nonmalignancy and malignancy group, respectively. The length of hospitalization remained significantly longer in the malignancy group (8.8 [SD = 12.0] vs 6.3 [SD = 6.6] days, p = 0.01). The proportion of patients with severe LV impairment on presentation also remained significantly higher in the malignancy compared with the nonmalignancy group (31.4% vs 15.2%, p = 0.003).

Subgroup analyses for patients with history of chemotherapy and/or metastatic disease was also conducted for

Table 2
In-hospital outcomes

Variable	All patients (n = 318)	Malignancy		p Value
		No (n = 237)	Yes (n = 81)	
Cardiogenic Shock	67 (21%)	49 (21%)	18 (22%)	0.89
Noninvasive positive pressure ventilation	52 (16%)	36 (15%)	16 (20%)	0.43
Mechanical ventilation	54 (17%)	39 (17%)	15 (19%)	0.8
Intra-aortic balloon pump	44 (14%)	33 (14%)	11 (14%)	1
Cardiac arrest	11 (4%)	5 (2%)	6 (7%)	0.04
Death	13 (4%)	8 (3%)	5 (6%)	0.33
Length of intensive care unit stay (days)				
Median (IQR)	0 (0−3)	0 (0−2)	1 (0−4)	0.06
Mean (SD)	2.2 (4.9)	1.7(3.4)	3.3 (7.7)	
Length of hospitalization (days)				
Median (IQR)	5 (3−9)	4 (3−8)	7 (4−13)	0.001
Mean (SD)	7.8 (9.4)	6.8 (7.4)	10.6 (13.5)	

IQR = interquartile range; SD = standard deviation. Data are expressed as number (percentage) or as mean (standard deviation)/median (interquartile range).

parameters that showed statistical significance. No statistically significant differences were observed except for patients with metastatic disease having a faster heart rate on presentation (Supplementary Tables 1,2,3). We conducted analysis to compare AA to non-African Americans (non-AA) in the whole TC sample and sample stratified by malignancy versus nonmalignancy. We further tested effects of ethnicity between malignancy groups through regression models with ethnicity, malignancy, and interaction between the two as covariates. In the whole TC sample, AA were more likely to suffer in-hospital cardiac arrests compared with non-AA patients (10 [6.62%] vs 1 [0.76%] arrests, odds ratio 9.29 [confidence interval 1.17 to 73.5]), respectively. Asystole was identified as the cause of death in 3 patients, pulseless electrical activity in 3, ventricular tachycardia in 2, torsades de pointes in 1 and the rhythm was not documented in 2 patients. In the malignancy group, AA patients were more likely to have a cardiac arrest (5 [11.6%] vs 1 [3.03%] arrests, odds ratio 4.21 [confidence interval 0.47 to 37.9]), respectively. In the nonmalignancy group 5 (4.63%) AA patients had a cardiac arrest whereas there were no cardiac arrests in the non-AA patients, thus a calculation of interaction effect was not statistically feasible. In the whole TC sample, AA patients had longer hospitalizations compared with non-AA patients (6 [IQR 3 to 10] vs 5 [IQR 3 to 8] days, $p = 0.02$, respectively). The interaction effect between ethnicity and malignancy for length of hospitalization was not statistically significant ($p = 0.62$). There was no significant difference in the length of ICU stay between AA and non-AA across the whole TC sample. Although, AA patients with malignancy had significantly longer ICU stays compared with non-AA patients (2 [IQR 0 to 5] vs 0 [IQR 0 to 3 days, $p = 0.03$) the interaction effect of ethnicity and malignancy for length of ICU stay was not statistically significant ($p = 0.06$). Presenting heart rate and degree of LV impairment were not different in the whole group between AA and non-AA with no significant interaction effect with malignancy.

Discussion

Our results show that, in racially diverse population hospitalized with TC, history of cancer is associated with

Table 3
Imaging findings

Variable	All patients (n = 318)	Malignancy		p Value
		No (n = 237)	Yes (n = 81)	
Left ventricular dysfunction on presentation				
Mild (ejection fraction >40%)	60 (19%)	51 (22%)	9 (11%)	0.01
Moderate (ejection fraction 25%−39%)	196 (62%)	148 (62%)	48 (59%)	
Severe (ejection fraction <25%)	62 (19%)	38 (16%)	24 (30%)	
Left ventricular dysfunction at follow-up				
Mild (ejection fraction >40%)	20 (77%)	16 (76%)	4 (80%)	1
Moderate (ejection fraction 25%−39%)	42 (51%)	33 (54%)	9 (43%)	0.52
Severe (ejection fraction <25%)	10 (33%)	8 (38%)	2 (22%)	0.67
All degrees	72 (52%)	57 (55%)	15 (43%)	0.28
Time to follow-up echocardiogram (days) for categories of left ventricular dysfunction on presentation				
Mild (ejection fraction >40%)	5.6 (9.8)	4.3 (9.5)	11.2 (10.4)	0.16
Moderate (ejection fraction 25%−39%)	12 (17.7)	12.4 (19.3)	10.7 (12.2)	0.70
Severe (ejection fraction <25%)	5.4 (6.0)	5.3 (6.6)	5.7 (4.6)	0.88
All degrees	9.3 (14.9)	9.3 (16.1)	9.5 (10.5)	0.96
Ventricular wall motion abnormality				
Apical	251 (79%)	183 (77%)	68 (84%)	0.65
Mid-ventricular	12 (4%)	10 (4%)	2 (3%)	
Basal	9 (3%)	8 (4%)	1 (1%)	
Combined	46 (14%)	36 (15%)	10 (12%)	

Data are expressed as number (percentage) or as mean (standard deviation).

worse in-hospital outcomes. Patients with history of malignancy had higher rates of in-hospital cardiac arrests, longer hospitalization, and lower mean LVEF on presentation. The observed association remained significant after controlling for sepsis, a potential confounder in this population. To our knowledge, this is the largest study investigating the relation between malignancy and TC that uses chart-review for data collection and adjudication. It is also the first to include a significant proportion of AA, and to control for sepsis as a potential confounder that can cause both TC[14] and nonspecific septic cardiomyopathy.[15]

We observed higher rate of cardiac arrests in the TC patients with cancers compared with previous reports.[4,6] High proportion of AA, in whom higher risk of complications has been reported compared with Caucasians,[8] may have accounted for the difference. Indeed, in our study AA had significantly more cardiac arrests in the whole cohort, as well as in both the malignancy and nonmalignancy groups compared with non-AA patients. We used the Mayo Clinic criteria, rather than Madias' criteria[16] used by Girardey et al[4] that may have led to the inclusion of more severely ill patients, particularly patients with severely reduced LVEF (<25%) which accounted for 19.5% of our population. This might have increased the risk of life-threatening arrhythmias as reported in a previous study in which low LVEF on presentation was a predictor of more in-hospital complications in TC patients.[1] Our findings of longer hospitalization in TC with cancer are consistent with those of recent ICD-9 based analyses.[17] We also showed longer length of hospitalizations in AA compared with non-AA patients with TC. Other studies did not identify differences in length of hospitalization,[5,6] however, smaller cohorts and lack of racial diversity may account for the observed findings. In agreement with the data by Sattler et al[6] but not with those by Girardey et al and Moller et al[4,5] we found lower LVEF in patient with TC and cancer compared with those without. This may be due to difference in the patient populations included in the analyses as well as methodological aspects. For instance, we included LVEF measured by angiography if an echocardiogram was not available within the first 2 days to get an estimate of the true LVEF on presentation whereas other studies only recorded LVEF by echocardiogram, which may have been delayed. Finally, in our study, the prevalence of cancer in TC patients (25.5%) greatly exceeds that of the United States general population[18] and is consistent with observations in previous studies,[4–6,19] confirming the association of TC and cancer also in a racially diverse population with AA predominance.

Several theories linking cancer and TC pathogenesis might help explain the observed worse outcomes in the malignancy group. A recent study in rat in-vivo model identified a switch in myocardial β-2 adrenergic G-protein signaling, from Gs (stimulatory) to Gi (inhibitory) in response to high doses of epinephrine, as a potential mechanism of the paradoxical negative inotropic effect of high levels of circulating epinephrine.[20] This functional response was greater in the apical as compared with basal myocytes suggesting that apical hypokinesis characteristic of TC may be explained by higher apical sensitivity to epinephrine.[20] Catecholamines play a role in the pathogenesis of several cancers[21] and hypersensitivity of catecholamine receptor has been reported in cancer patients.[3] In addition to epinephrine sensitivity hypothesis, inflammatory response was proposed to have a role in the pathogenesis of TC through increased expression of p38-activated protein kinase, characteristic of inflammatory state, and resulting in increase in β-adrenergic receptor signaling.[22,23] Higher leukocyte count and C-reactive protein levels were observed in TC patients with malignancy as compared with those without, suggesting a higher degree of inflammatory response.[4] Finally, similarities in genetic polymorphism such as variants in BAG3 (bcl2-associated athanogene 3) have been reported in cancer and TC patients possibly suggesting common genetic susceptibility.[24] Of interest, in a recent study BAG3 variants were associated with worse heart failure outcomes in individuals with cardiomyopathy and high prevalence of BAG3 variants were present in African Americans but not individuals of European ancestry.[25]

Our analysis of the effect of ethnicity on TC outcomes and its interaction with malignancy was exploratory and hypothesis-generating as our study was underpowered for this comparison. Nevertheless, we believe that the observed findings point to the need to further investigation. In the whole studied TC population, AA patients had more in-hospital cardiac arrests compared with other ethnicities. This was not previously reported and is consistent with previous literature suggesting worse outcomes in TC patients of AA descent[8] and a recent study showing more sudden cardiac deaths in AA that was not explained by socioeconomic and cardiovascular risk factors.[26] Our finding of longer hospitalization in AA is consistent with a previous study by Dias et al[8] further adding to the available literature suggesting racial differences in TC.[8,9] Interestingly, when comparing AA versus non-AA patients within the malignancy group, AA patients were found to suffer more in-hospital cardiac arrests and have longer ICU stays. The later finding was not observed when comparing AA vs non-AA across the whole sample suggesting a possible influence of ethnicity on outcome in this particular subset of TC patients. Our findings of racial differences can be explained by several hypotheses. A study by Kurnik et al found racial variations in hemodynamic response to stressors where AA had exaggerated heart rate increment compared with Caucasians possibly due to variation in genes regulating sympathetic activity.[27] Increased plasma levels of endothelin-1[28] and reduced coronary flow reserve[29] were observed in acute TC, suggesting a role for coronary microcirculation dysfunction in TC pathogenesis. Interestingly, in a study by Kalinowski et al AA were found to have racial predisposition to endothelial dysfunction by enhanced nitric oxide inactivation[30] possibly explaining their observed worse outcomes in TC.

Several limitations of our study should be acknowledged. First, we analyzed data from a single center electronic health record and had incomplete data regarding the time of cancer diagnosis relative to the presentation for TC, as well as cancer stage and the type of cancer treatment. Follow-up data were limited to the information available in the hospital health record.

In conclusion, our analysis of a racially diverse population hospitalized with a diagnosis of TC shows that

history of cancer is associated with lower LVEF on presentation, longer hospitalization and higher rate of in-hospital cardiac arrests. Future prospective study is needed to investigate whether cancer diagnosis and/or treatment contribute to the association with TC and its impact on cardiovascular outcomes. In addition, further genetic and mechanistic studies are needed to provide insight into racial differences in TC patients, particularly those with malignancies.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjcard.2018.11.054.

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