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The Long-Term Clinical Outcome of Posttraumatic Stress Disorder With Impaired Coronary Distensibility

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ABSTRACT

Objective: Coronary Distensibility Index (CDI) impairments reflect endothelial-dependent process associated with vulnerable-plaque composition. This study investigated the relation of impaired CDI with posttraumatic stress disorder (PTSD) and their predictive value for major adverse cardiovascular events (MACE).

Methods: This study involved 246 patients (age = 63[10]years, 12% women) with (n = 50) and without (n = 196) PTSD, who underwent computed tomography angiography to determine coronary artery disease and CDI. Extent of coronary artery disease was defined as normal, nonobstructive (<50% luminal stenosis), and obstructive (>50%). Incidence of MACE, defined as myocardial infarction or cardiovascular death, was documented during a mean follow-up of 50 months. Survival regression was employed to assess the longitudinal association of impaired CDI and PTSD with MACE.

Results: A significant inverse correlation between CDI and Clinical Global Impression Severity scale of PTSD symptoms was noted (r^2 = .81, p = .001). CDI was significantly lower in patients with PTSD (3.3[0.2]) compared with those without PTSD (4.5[0.3]), a finding that was more robust in women (p < .05). Covariate-adjusted analyses revealed that the relative risk of MACE was higher in patients with PTSD (hazard ratio [HR] = 1.56, 95% CI = 1.34–3.14) and those with impaired CDI (HR = 1.95, 95% CI = 1.27–3.01, per standard deviation lower CDI value). There was also a significant interaction between PTSD and impaired CDI (HR = 3.24, 95% CI = 2.02–5.53).

Conclusions: Impaired CDI is strongly associated with the severity of PTSD symptoms. Both impaired CDI and PTSD were independently associated with an increased risk of MACE during follow-up, and evidence indicated an interaction between these two factors. These findings highlight the important role of CDI in identifying individuals with PTSD at risk for MACE.

Key words: computed tomography angiography, Coronary Distensibility Index, major adverse cardiovascular events, posttraumatic stress disorder.

INTRODUCTION

The lifetime prevalence of combat posttraumatic stress disorder (PTSD) in the United States is 5% to 20% (1,2) and is even more prevalent in military personnel serving in Iraq and Afghanistan (2). In addition to debilitating physical and psychological health decline, PTSD is associated with increased rates of multiple medical disorders as well as many biomarker abnormalities (3,4). Many studies have linked PTSD to cardiovascular diseases and myocardial infarction (MI) (3,5–7). We previously reported the independent association of PTSD with the presence and severity of coronary artery calcium (CAC)—an irreversible stage of atherosclerosis—that predicts mortality (8). However, a conclusive link between PTSD and reversible stages of atherosclerotic coronary artery disease (CAD) has not been made.

Impaired Coronary Distensibility Index (CDI), a key initial reversible marker of inflammation, contributes to all stages of inflammation and atherosclerosis that are associated with reduced cerebral blood flow and increase of oxidative stress, blood-brain barrier disturbances, autonomic nervous system dysfunction, upregulation of proinflammatory genes, down-regulation of atheroprotective genes, neural apoptosis, and pathogenesis of cerebro- and cardiovascular events (9–15).

The Veteran Health Administration, the largest health care system in the nation, provides integrated comprehensive physical and psychological assessment of all veterans in the primary care setting. This offers a unique opportunity to evaluate the relationship between PTSD and CDI.

The current study investigates the relationship of PTSD with coronary artery distensibility, measured by CTA, as well as with major adverse cardiovascular events (MACE).

CAD = coronary artery disease, **CDI** = Coronary Distensibility Index, **CTA** = computed tomography angiography, **MACE** = major adverse cardiovascular events, **PTSD** = posttraumatic stress disorder

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METHODS

After our first study of 637 consecutive veterans without known CAD who underwent noncontrast computed tomography between 2006 and 2008, which showed a significant association of PTSD with CAC, we conducted this retrospective cohort study, using a nested case-control design, which includes 246 patients, aged 63(10)years, 12% women, with (n = 50) and without (n = 196) PTSD. All consecutive patients with and without PTSD, who were free of other major psychiatry disorders, and without known CAD, who underwent clinically indicated contract-enhanced cardiac computed tomography angiography (CTA) during 2008–2010, were included. The incidence of MACE was assessed for a mean of 50 months after their CTA. Age-, sex-, and enrollment time–matched controls were randomly selected from the pool of eligible controls without PTSD, to form an incidence density sampled risk set for the index case. The presence of CAD and its severity, as well as their CDI, were measured using CTA images. The study protocol of analyses of existing data and waiver for consent was approved by the institutional review board committee at Hines and Greater Los Angeles VA Healthcare Systems, respectively.

Definition of PTSD

PTSD diagnosis was established using the criteria of the DSM-IV using ICD and DSM-IV codes. Those patients with positive Clinician-Administered PTSD Scale and PTSD Checklist Military scores, verified by psychiatrist-structured interview, were classified as having PTSD. The Cronbach's α coefficient value was .90.

Control Ascertainment

Using SAS statistical programming, 192 age-, sex-, and enrollment time–matched controls were randomly selected, from the pool of 920 eligible controls without PTSD who underwent cardiac CTA, using a nested case-control design.

Cardiac CTA

β blockers were administered for pulses greater than 65 beats per minute. A test intravenous bolus of 15 ml of contrast agent was given, followed by 20 ml of normal saline flush at a rate of 4.5 ml/s. Using a dual-head power injector (Stellant, Medrad, Indianola, PA), a prospective ECG-gated cardiac CT angiography was performed with a tri-phasic consecutive injection sequence beginning with 50-ml nonionic intravenous contrast material (Iopamidol 370; Bracco Diagnostics, Plainsboro, NJ) injected at a rate of 5.0 ml/s followed by 50 ml of a mixture of 60% contrast and normal saline and ending with a 50-ml flush of normal saline. Contrast was injected through an 18- to 20-gauge angiocatheter in an antecubital vein. The M (SD) heart rate during the scan was 56(3) beats per minute.

Data Acquisition, CAD, and CDI Measurement

A snapshot pulse acquisition axial ECG-triggering mode with prospective gating using the 64-Multidetector Computed Tomography (MDCT) Lightspeed VCT scanner (General Electric Healthcare Technologies, Milwaukee, WI) was used for all patients. Imaging was started 1 inch above the left main ostium and continued to 1 inch below the bottom of the heart. The following imaging and reconstruction parameters were applied: data acquisition collimation 0.625 mm × 64 = 4 cm; 120 kVp; 220–670 mAs; pitch 0.18–0.24 (depending on heart rate); rotation time 0.35 s; slice width 0.625 mm; matrix 512 × 512; and pixel size 0.39 mm^2. ECG-triggered dose modulation with padding was applied in each case with 400 to 600 mA in 70% to 80% R-R interval. CAD was classified as normal, nonobstructive (stenosis 1%–49%) and obstructive (stenosis ≥50%). The cross-sectional area (CSA) of the left anterior descending artery was measured, using the curved multiplanar reformations and lumen view, from 5% to 95% of the R-R interval, in 10% increments. CDI was defined as the following: [(early diastole − mid diastole lumen CSA)/(lumen CSA in mid diastole × central pulse pressure) × 1000].

Clinical Global Impression–Severity of Illness Scale

The Clinical Global Impression–Severity of Illness Scale (CGI-S) is rated on a 7-point scale, measuring the severity of illness at baseline before receiving a treatment. The range of responses are from 0 (not assessed), 1 (normal), 2 (borderline ill), 3 (mildly ill), 4 (moderately ill), 5 (markedly ill), 6 (severely ill), to 7 (among the most extremely ill patients). The CGI-S of traumatic reminder and overall PTSD symptoms at the time of cardiac CTA was measured (16).

Long-Term End Points

For MACE, the long-term end points were defined as occurrence of cardiovascular mortality and MI and verified by the Social Security Death Index. Related data were obtained from electronic medical records including VA Beneficiary Identification and Records Locator system, VA Centers for Medicare & Medicaid Services vital status, Social Security Administration death index, and the National Death Index Data. MACE was ascertained by healthcare providers in all patients.

Statistical Analysis

All continuous data are presented as a M (SD), and all categorical data are reported as a percentage or absolute number. χ^2 and t tests were used to assess differences between groups. Mixed regression was employed to assess the relation of CDI and extent of coronary atherosclerosis with PTSD. Multivariable mixed regression analyses were employed to assess the relation of impaired CDI and PTSD with MACE, with and without adjustment for cardiovascular risk factors. The main and interaction effects were analyzed using regression models. The relative risk of MACE and CIs were calculated using a bootstrapping technique. Using multivariate mixed regression analyses, risk factor–adjusted survival curves were constructed for normal versus impaired CDI with and without PTSD. Receiver operating characteristic (ROC) curves were constructed, and the area under the ROC curve was calculated to assess the ability of each model to predict MACE. All statistical analyses were performed using SAS Version 9.2 (SAS Institute Inc, Cary, NC, http://www.sas.com) and SPSS Version 24 (SPSS Inc, Chicago, IL, http://www.spss.com).

RESULTS

Demographic and conventional risk factors are presented in Table 1. There were no significant differences between group (i.e., patients with and without PTSD) in terms of age, sex, diabetes mellitus, smoking status, hypertension, hypercholesterolemia, family history of premature CAD, and mental health disorder. The prevalence of nonobstructive CAD was higher in the PTSD group, compared with those without PTSD. We found a significant reverse association between impaired CDI and PTSD traumatic reminders (r^2 = .81, p = .001), as well as between CDI and the severity of PTSD symptoms measured by CGI scale (r^2 = .59, p = .001), in patients with PTSD (Fig. 1).

CDI was significantly lower in patients with PTSD, compared with those without PTSD (p < .001), and this difference was more pronounced in women (Fig. 2A). CDI decreased proportionally with the severity of CAD (Fig. 2B), a correlation that was significantly more robust in patients with PTSD (p < .05).

Table 2 shows that the likelihood ratio of PTSD was 1.45 times higher for CTA diagnosed coronary disease and 1.75 folds higher for each standard deviation decrease in CDI, compared with patients without PTSD (p < .05). In addition, a significant link between impaired CDI and severity of CTA diagnosed CAD with PTSD was observed; the likelihood ratio of PTSD was 5.1 and 7.5 times higher in impaired CDI and nonobstructive CAD, and obstructive CAD, respectively (p < .001).

TABLE 1. Clinical Characteristics of Individuals With and Without PTSD

Model	Individuals Without PTSD (n = 196)	Individuals With PTSD (n = 50)	p
Age, M (SD)	62(9)	61(10)	.88
Sex (male)	70% (137)	74% (37)	.79
Diabetes mellitus	15% (29)	18% (9)	.91
Hypertension	53% (104)	56% (28)	.90
Hypercholesterolemia	52% (102)	58% (29)	.84
Family history of CHD	55% (108)	62% (31)	.71
Smoker	38% (72)	42% (21)	.92
Body mass index, M (SD)	28.2(4.7)	27.8(4.5)	.65
Family history of MHD	25% (49)	30% (15)	.65
CGI for PTSD symptoms, M (SD)	1.2(1)	5.5(1)	.001
Psychiatry hospitalization	0	0	—
CDI, M (SD)	4.5(0.3)	3.3(0.2)	.001
Diseased coronaries	50% (98)	64% (32)	.03
Obstructive CAD	31% (30)	41% (13)	.20
MACE (%)	5.6% (11)	28% (14)	.001

PTSD = posttraumatic stress disorder; CHD = coronary heart disease; MHD = mental health disorder; CDI = Coronary Distensibility Index; Diseased Coronaries = coronary artery obstruction of 1%–99%; CAD = coronary artery disease; MACE = major adverse cardiovascular events.

Table 3 shows that PTSD and CDI are independent predictors of MACE after adjustment for age, sex, conventional risk factors, and CTA diagnosed CAD ($p < .05$). The hazard ratio of MACE was 56% higher in PTSD, and 95% higher with each SD decreases in CDI ($p < .001$). Regression analyses revealed a significant link between PTSD and impaired CDI. The risk of MACE was 234% higher in patients with impaired CDI and PTSD, compared with those without PTSD and within normal CDI ($p = .001$).

Figure 3 displays the ROC curves for the study's data. We found a significant prognostic value of PTSD, CAD, CDI, and their combination in terms of predicting MACE. The prognostic value was higher with the combination of PTSD and impaired CDI, with the highest prognostic value being observed with the combination of PTSD, impaired CDI, and CTA-diagnosed coronary diseases ($p = .001$).

Finally, Figure 4 presents evidence in support of a direct link of PTSD and impaired CDI with MACE over time. After adjusting for risk factors, the event free survival was significantly lower in patients with PTSD who also had impaired CDI (67.5%) compared with the reference group of patients without PTSD and within normal CDI (98%, $p = .001$). In addition, it shows that PTSD with preserved CDI is associated with favorable outcomes compared with PTSD with impaired CDI ($p = .001$).

DISCUSSION

The present study supports several novel findings: (1) impaired CDI is strongly associated with the severity of PTSD symptoms, especially with traumatic reminders; (2) PTSD and CDI are independent predictors of MACE; (3) there is a significant link between PTSD and impaired CDI with increased risk of MACE; (4) the impairment of CDI in patients with PTSD substantially increases the risk of MACE; and (5) the combination of impaired CDI, diseased coronaries, and PTSD provides the highest predictive value for identification of at-risk individuals for MACE.

There is compelling evidence that PTSD is associated with multiple medical and mental disorders (3) through alterations in inflammatory state (4,17), increased coagulation factors (18,19), increased platelet activity (20), increased lipid levels and lipid reactivity (21), dysregulation of the hypothalamic-pituitary-adrenal axis, impaired vascular function, and CADs (22–26). Our previous study showed that PTSD was an independent predictor of presence and extent of CAC—which is an advanced irreversible stage of CAD—and independently predicts mortality ($p = .001$).

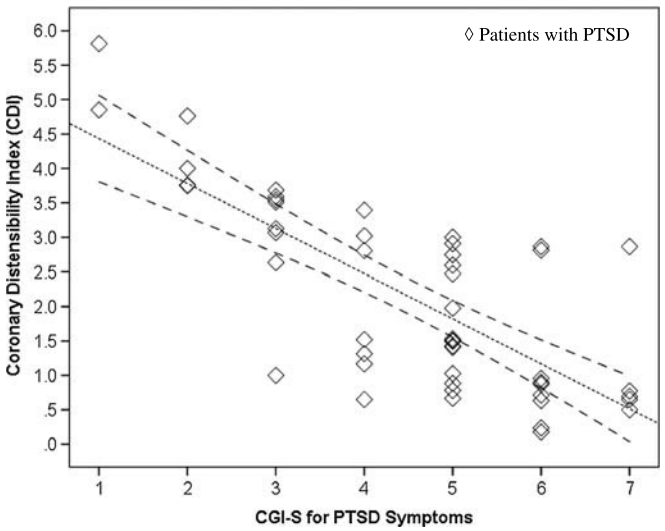


FIGURE 1. The inverse relation of CDI with the severity of PTSD symptoms measured by CGI-S scale. Diamonds represent patients with PTSD.

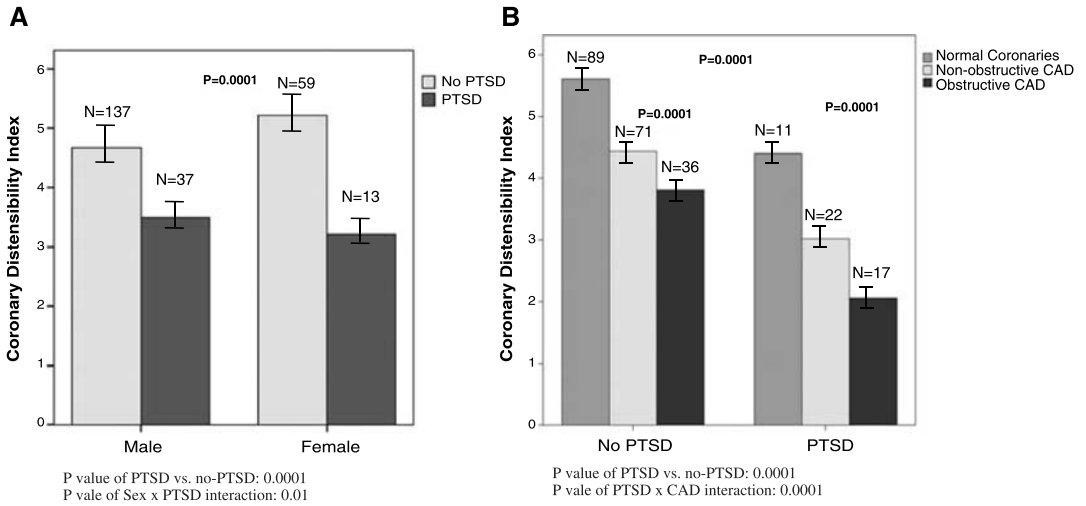


FIGURE 2. A, Relation of CDI with Posttraumatic Index in both sexes. B, Relation of CDI with the severity of CAD in individuals with and without PTSD.

After adjustment for risk factors, relative risk of death was 1.48 (95% CI = 1.03–2.91, p = .001) times higher in patients with PTSD and CAC score of higher 0 compared with patients without PTSD and CAC score equal to 0 (8). Previous studies investigated the relation of vascular dysfunction, an early reversible stage of atherosclerosis, with PTSD. Grenon et al. (27) compared the vascular function measured by flow-mediated vasodilation of the brachial artery in 214 veterans with and without PTSD and reported that PTSD remained independently associated with lower flow-mediated vasodilation of the brachial artery after adjustment for risk factors (p = .0005). A similar association between e-Selectin, soluble intercellular adhesion molecule 1 (s-ICAM-1), vascular cell adhesion molecule 1 (v-CAM-1) plasma levels, and the presence of PTSD was noted (28,29). The current study confirms previous studies, provides evidence that impaired CDI is associated with PTSD and its severity independent of risk factors and CAD, and independently predicts MACE in at-risk individuals.

TABLE 2. The Association of PTSD With Impaired CDI, CAD Severity, and Clinical Variables

Model	PTSD
Age, y	1.02 (0.91–1.05), p = .54
Sex, male	1.51 (0.13–2.57), p = .48
Hypertension	1.69 (0.91–6.36), p = .22
Hyperlipidemia	1.64 (0.76–3.53), p = .21
Diabetes mellitus	1.54 (0.67–2.45), p = .32
Family history of CHD	1.12 (0.22–5.91), p = .78
Family history of MHD	1.52 (0.13–1.71), p = .25
CTA diagnosed coronary diseases	1.45 (1.10–3.25), p = .03
Each standard deviation decreases in CDI	1.75 (95% CI = 1.23–2.56), p = .002
Impaired CDI and nonobstructive CAD*	5.1 (95% CI = 2.5–8.8), p = .01
Impaired CDI and obstructive CAD*	7.5 (95% CI = 2.3–15.2), p = .001

PTSD = posttraumatic stress disorder; CHD = coronary heart disease; MHD = mental health disorder; CTA = computed tomography angiography; CDI = Coronary Distensibility Index; CAD = coronary artery disease.

Multivariate mixed regression analysis.

Data present adjusted odds ratios using patients without PTSD as reference group.

Impaired CDI: CDI below median of 3.75.

Adjusted for age, sex, hypertension, hyperlipidemia, diabetes mellitus, family history of CHD, and MHD.

* Interaction analysis.

TABLE 3. Association of PTSD, CDI, and Their Combination With MACE During Follow-Up

Model	Hazard Ratio of MACE (95% CI)
Age, y	1.08 (0.99–1.17), p = .06
Sex (male)	1.41 (0.39–6.16), p = .54
Hypertension	1.48 (0.39–5.63), p = .55
Hyperlipidemia	1.86 (0.49–7.35), p = .35
Diabetes mellitus	1.52 (0.11–2.62), p = .46
Family history of CHD	1.52 (0.28–2.62), p = .41
Family history of MHD	1.30 (0.20–2.51), p = .59
CTA diagnosed coronary diseases	1.75 (1.05–6.45), p = .04
PTSD	1.56 (1.34–3.14), p = .001
Each SD decrease in CDI	1.95 (1.27–3.01), p = .001
PTSD and each SD decrease in CDI*	3.24 (2.02–5.53), p = .001

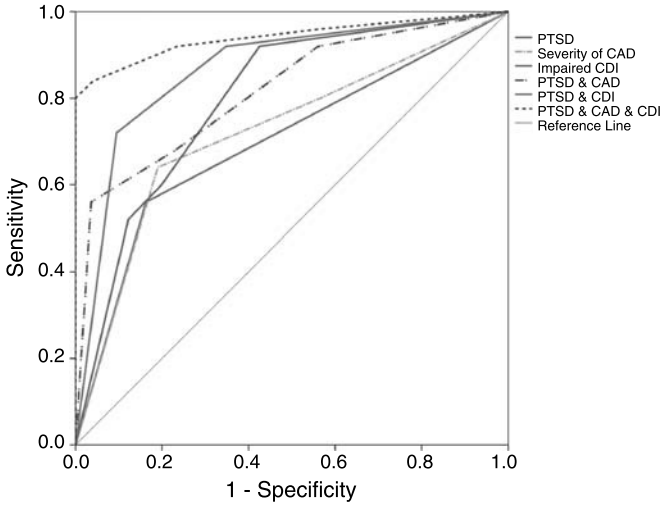
MACE = major adverse cardiovascular event; CHD = coronary heart disease; MHD = mental health disorder; CTA = computed tomography angiography; PTSD = posttraumatic stress disorder; CDI = Coronary Distensibility Index.

Multivariate mixed regression analyses.

Data present covariate-adjusted hazard ratios and 95% CIs.

* Interaction analysis.

Adjustment for age, sex, hypertension, hyperlipidemia, diabetes mellitus, family history of CHD and MHD, and CTA diagnosed coronary diseases.



Model	AUC (±SE)	95%CI	P value
PTSD	0.69 (0.01)	0.58 - 0.82	0.001
Severity of CAD	0.72 (0.01)	0.61 - 0.84	<0.001
Impaired CDI	0.79 (0.01)	0.71 - 0.86	<0.001
PTSD & CAD	0.82 (0.01)	0.72 - 0.90	<0.001
PTSD &Impaired CDI	0.87 (0.01)	0.79 - 0.94	<0.001
PTSD &Impaired CDI & CAD	0.94 (0.01)	0.89 - 0.99	<0.001

FIGURE 3. ROC curves to assess the prognostic value of PTSD, CAD, CDI, and their combination models for the prediction of MACE.

Traumatic reminders are core symptoms of PTSD that are associated with distress-related autonomic dysregulation, hyperarousal symptoms, negative affectivity, and poor neurological sequelae (30–34). Previous studies have reported that intrusive re-experiencing of traumatic events is associated with higher levels of C-reactive protein, an increase in salivary α-amylase, an increase in extracellular signal-regulated kinase in the ventral hippocampus, and an activation of the basolateral amygdala (30–32). Our findings confirm previous studies and provide evidence that there is a strong association between PTSD traumatic reminders and impaired CDI that predicts MACE independent of conventional risk factors and CAD, suggesting a potential mechanism by which traumatic stress translates into chronic inflammation in PTSD.

Clinical Application

The appreciation for a role of inflammation and vascular dysfunction in patients with PTSD has increased in light of recent studies (27–32). The risk of cardiovascular mortality significantly increases in patients with PTSD without known CAD independent of risk factors (8,22–25). The current study is the first to (1) make a direct association of impaired CDI with the presence and severity of PTSD, (2) prove PTSD independently associated with MACE, especially in those with impaired CDI, and (3) associate PTSD with preserved CDI with a favorable outcome.

Although many vascular function and inflammatory biomarkers experience substantial diurnal, spatial, temporal variability and operator dependency (35–37), CDI has low variability and is

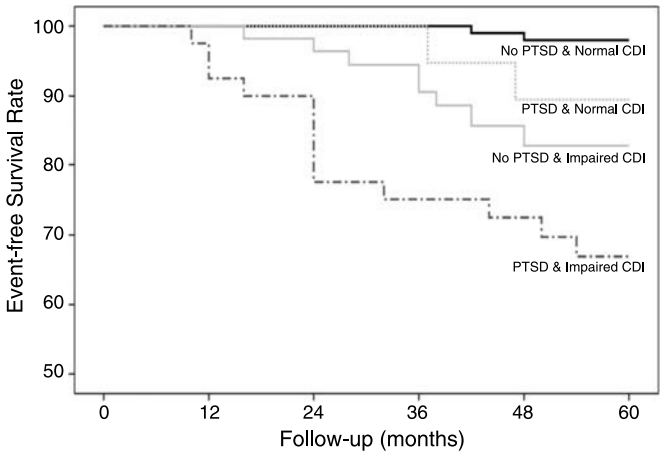


FIGURE 4. Risk-adjusted event free survival rate across individuals with and PTSD and impaired CDI (multivariate mixed regression analysis).

measured through an operator independent, standardized, and automated protocol (38). CDI could thus serve as a reliable test to identify individuals with PTSD at risk for MACE. Finally, the strong correlation of impaired CDI with the severity of traumatic reminders emphasizes its potential role in the early management of and in monitoring responses to therapy in at-risk individuals with PTSD.

Study Limitations

This study has several limitations. Veterans have disproportionately high rates of mental disorders and incidences of CAD compared with the general population in the United States. As a result, the conclusions of this study might not be applicable to the general population (39,40). Although the study population was mainly composed of male veterans, bootstrapping analyses revealed a less than 3% bias in estimating the relation of PTSD and impaired CDI with MACE in both men and women, after having the sample size increased to 100,000. The absence of standardized Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), trauma index, and reminder inventories are further limitations of this study. The lack of such measure could statistically be biasing the findings between PTSD, CDI, and MACE toward the null hypothesis. Further prospective studies are needed to evaluate the role of CDI in traumatic reminder occurrence and its effect on monitoring response to therapy and outcome of individuals with PTSD.

CONCLUSIONS

The severity of PTSD traumatic reminders is associated with impaired CDI. Furthermore, there is a significant link between PTSD and impaired CDI in predicting MACE, independently of age, sex, and other conventional risk factors. The combination of impaired CDI with PTSD provided incremental prognostic value in the prediction of MACE in at-risk individuals. These results strongly support an important role of impaired CDI as a first step in the continuum of the actual manifestations of coronary atherosclerosis and neuroinflammation in PTSD. They highlight the important role of CDI assessment for early identification and management of at-risk individuals with PTSD.

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