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The Prognostic Value of Total Antioxidant Capacity in Patients with Acute Coronary Syndrome

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Abstract

Background: Antioxidants are known to play a role in the prevention of coronary artery disease (CAD) whereas oxidative stress contributes to endothelial dysfunction and the development of atherosclerosis. Studies have reported low levels of total antioxidant capacity (TAC) in ACS patients. The objective of our study was to evaluate levels of TAC between different populations and its prognostic value. *Methods and Results:* A total of 163 subjects were included in the study consisting of Control (N=21), Chronic Stable Angina (CSA) (N=21), Non-ST-elevation myocardial infarction (NSTEMI) (N=57) and ST-Elevation Myocardial Infarction (STEMI) (N=64) patients between the period March 2017 to April 2018. Antioxidant levels from the plasma samples were measured by Trolox Equivalent Antioxidant Capacity (TEAC) assay. Patients were also followed up at different time intervals to identify the occurrence of major adverse cardiac events (MACE). All statistical analyses were performed using SPSS software version 16.0 (SPSS Inc., Chicago, IL). The concentration between the 3 groups varied significantly (p=0.002) with an average trolox concentration of 1.562 mM as observed in Control, 2.05 mM in CSA and 2.55 mM in ACS subjects. We also observed a negative correlation between TAC and cardiac markers, creatine phosphokinase (CPK) (r= -0.194, p=0.040) and Creatine kinase-MB (CK-MB) (r= -0.232, p=0.013). However, TAC levels did not provide any prognostic information [AUC = 0.458, p = 0.630, 95% CI (0.297-0.619)]. *Conclusion:* TAC levels did not provide any prognostic value. Larger sample sizes are required to assess their role.

Keywords: ACS; MACE; TEAC Assay; TAC.

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Introduction

Coronary artery disease (CAD) is a multifactorial complex disease which remains to be one of the leading causes of morbidity and mortality worldwide. Acute Coronary Syndrome (ACS) is a sub-group of CAD and is an umbrella term consisting of three different clinical entities: ST Elevation Myocardial Infarction (STEMI), Non-ST Elevation Myocardial Infarction (NSTEMI) and, Unstable Angina (USA). Atherosclerosis is the main underlying pathophysiology which leads to CAD. Several factors lead to the formation of atherosclerosis such as endothelial dysfunction, lipid deposition in the vessels, damaging immune responses and vascular smooth cells proliferation [1]. There is an increasing plethora of evidence supporting the role of oxidative stress in the origin

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of atherosclerosis. Oxidative stress is the imbalance between the prooxidant and the antioxidant system leading to either increased free radicals or reduced activity of the antioxidant systems. Reactive oxygen species (ROS) are known to damage vascular cells and cardiac myocytes and contribute to atherosclerosis leading to ACS. They damage biomolecules such as protein, nucleic acids, and lipids. ROS molecules are known to produce protein and deoxyribonucleic acid (DNA) adducts which aid in vascular inflammation [2].

Owing to the indisputable role of oxidative stress in ACS patients, it is essential to develop cheaper and efficient tools to assess the redox status of a patient. A test to globally measure the total antioxidant capacity (TAC) levels, Trolox Equivalent Antioxidant Capacity (TEAC) is one of the methods utilized to determine TAC levels. It is a colorimetric method based on the change of the characteristic color of a more stable 2,2′-azinobis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radical cation by antioxidants [3]. The aim of our study was to assess the levels of TAC and three cardiac biomarkers, namely, Galectin-3, Matrix metallopeptidase 9 (MMP-9), and soluble suppression of tumorigenicity 2 (ST2), in different study groups and determine if their concentration level can aid in predicting major adverse cardiac events (MACE) in ACS patients.

Methods

This was a single center, prospective cohort study conducted between March 2017 to August 2018 at the Department of Clinical Pharmacology and Department of Cardiology, SRM Medical College Hospital and Research Centre, Kattankulathur, Kancheepuram, India. We included subjects who were diagnosed with STEMI (N=64), NSTEMI/USA (N=57), Chronic stable angina (N=21) and healthy volunteers (N=21). STEMI was defined as "presence of symptoms of myocardial ischemia along with persistent ST elevation and release of myocardial necrosis biomarkers". Based on the similarity of pathogenesis and clinical presentation, NSTEMI and USA were considered together as NSTEMI patients. It was defined as "absence of persistent ST elevation and along with the release of myocardial injury marker in NSTEMI patients and no release of markers in unstable angina patients". Chronic stable angina was defined as "chest discomfort with a characteristic duration and quality and can be alleviated by rest or use of nitroglycerine" [4-6]. Healthy volunteers were individuals who did not have a history of significant medical illness. Exclusion criteria for ACS patients included the presence of evolved MI, malignancy, autoimmune diseases, and inflammatory diseases. Criteria for the exclusion of CSA patients included if they had previously experienced a myocardial infarction or cardiovascular revascularization, or if the chest pain was non-cardiac in nature.

We screened 302 subjects for all the study groups from which 79 patients were removed based on our exclusion criteria, whereas 11 patients were unwilling to provide consent for the study. In the end, 216 subjects participated in the study, out of which 14 subjects were lost during follow-up and

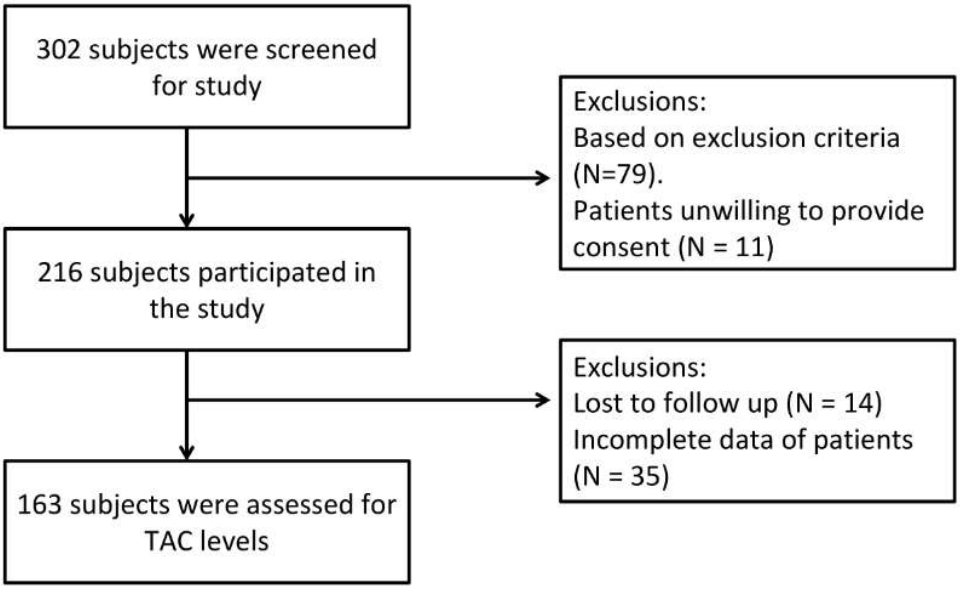


Fig. 1: Flowchart illustrating inclusion and exclusion of the study population.

we had incomplete data for 35 subjects. We assessed 163 subjects for our current study (Fig. 1).

Demographic and clinical parameters from the study subjects were recorded at the time of their admission which included their age, sex, body mass index (BMI) and waist to hip ratio. Blood tests were done on their samples at admission to determine their hemoglobin, total leukocyte count (TLC), packed cell volume (pcv), serum creatinine, blood urea and known cardiac enzymes like troponin-T and CK-MB (Creatine kinase-MB).

Presence of diabetes in study patients was determined by their clinical history and whether their level of fasting plasma glucose (FPG) was ≥126 mg/dL where fasting was defined as no caloric intake for ≥ 8 hours [7]. Other traditional cardiovascular risk factors such as hypertension, renal disease, family history of cardiac disease and sedentary lifestyle were also recorded. Based on a patients' clinical history and blood pressure, they were assessed for hypertension. Blood pressure of 140/90 mm Hg in individuals below 60 years and blood pressure of 150/90 mm Hg in individuals above 60 years was used as the definition of hypertension [8]. Chronic kidney disease (CKD) was assessed based on their history and eGFR (Estimated Glomerular filtration rate) values and was defined as kidney damage or GFR <60 mL/min/1.73 m^2 for ≥ 3 months. eGFR was calculated using Chronic kidney disease Epidemiology Collaboration equation (CKD-EPI) [9]. All current smokers, irrespective of the frequency and amount, were deemed as smokers. A patient was said to have a family history if any of their biological parents had a cardiac disease. Echocardiography also was performed to measure LVEF (Left Ventricular Ejection Fraction) and detect the presence of regional wall motion abnormality (RWMA) in patients. Coronary angiography (CAG) results were further used to calculate gensini score which is a coronary angiographic scoring system to determine the CAD burden.

The study protocol conforms to the principles of the Declaration of Helsinki and the Indian Council of Medical Research (ICMR) guidelines for biomedical research. The study was approved by the institutional ethics committee and informed consent was obtained from subjects for participation in the study.

Laboratory analysis

4 ml of peripheral venous blood samples of the patients under fasting conditions were obtained from the cubital vein into Ethylenediaminetetraacetic acid (EDTA) coated tube before coronary angiography. The plasma was isolated from the blood samples by centrifugation at 3000 rpm for 10 minutes and stored at -80°C until the day of analysis.

TAC level was determined by performing the TEAC assay (Trolox Equivalent Antioxidant Capacity) (Antioxidant assay kit, Cayman Chemical, MI, USA). We also measured three other biomarkers known to have a role in oxidative stress and atherosclerosis. Galectin-3, MMP-9 and sST2 levels were measured by Enzyme-linked immunosorbent assay (ELISA) using commercially available kits (Human Galectin-3 Quantikine ELISA kit, R & D Systems, MI, US; Human MMP-9 Quantikine ELISA kit, R & D Systems, MI, US; Human ST2/IL-33 R Quantikine ELISA kit, R & D Systems, MI, US) using manufacturer's recommendations. The readings were measured using a plate reader (Infinite F50, Tecan Group Ltd., Mannedorf, Switzerland). All the samples for the study were processed and analyzed at the Department of Clinical Pharmacology by personnel blinded to clinical characteristics and outcome of patients.

Follow-up

Patients were followed for a period of 1 month, 3 months, 6 months and 9 months after the initial event. They were assessed by telephonic interview at the end of the period to inquire about the occurrence of major adverse cardiac events (MACE) such as stroke, recurrent MI, re-hospitalization, and death.

Statistical Analysis

Statistical analysis of the study was performed using SPSS 16.0 software (SPSS Inc., Chicago, IL, USA). Normality of data was first identified by preparing histograms. Continuous variables were represented as the mean ± standard deviation (SD) for normally distributed data, whereas for non-normally distributed variables, it was expressed as the median and interquartile range (IQR). Categorical data were represented as the frequency with the percentage. Independent samples t-test or Mann Whitney U test was done to determine difference among continuous variables. Spearman's correlation coefficients were used to assess the correlations between TAC and other continuous variables. All Receiver Operating Characteristic (ROC) curve was plotted to determine the utility of

TAC to predict mortality in ACS patients. A p-value of 0.05 was considered statistically significant.

Results

One hundred sixty three (163) subjects were involved in our study which included ACS (n=121), CSA (n=21) and healthy volunteers (n=21). In the ACS study group, 64 subjects had STEMI and 57 subjects had NSTEMI/USA. The general demographic and clinical characteristics of the subjects are summarized in Table 1. LVEF was lower in STEMI compared to NSTEMI/USA and CSA. STEMI patients also consisted of a high number of patients with other comorbidities such as diabetes, hypertension, smoking and sedentary lifestyle. The occurrence of three-vessel disease was also higher in STEMI patients compared to other study groups.

Mean concentration of TAC levels varied between different groups with 1.56 ± 1.01 mM levels in STEMI patients, 2.03 ± 1.23 mM in NSTEMI/USA patients, 2.55 ± 1.34 mM in CSA patients, and 3.39 ± 2.40 mM in control subjects. STEMI patients demonstrated the lowest concentration of TAC with the levels increasing in groups as the severity of the disease lowered. The concentration was significantly different between CSA and STEMI patients (p=0.001) and STEMI and NSTEMI/USA patients (p=0.029).

A significant positive correlation was found between TAC and LVEF and MMP-9 (r=0.180, p=0.013 and r=0.264, p=0.007; respectively). However, there was no significant correlation

Table 1: Baseline Characteristics Including Demographics, Risk Factors and Laboratory Findings of Study Participants

Characteristics	STEMI (n=64)	Non-STEMI (n=57)	CSA (n=21)	p-value
Age, years	52.69 ± 11.31	57.82 ± 11.57	56.29 ± 7.88	0.035
Gender, % (Male)	59 (92.20)	32 (56.10)	10 (47.60)	0.0001
BMI, kg/m2	25.07 ± 2.97	25.98 ± 4.41	28.65 ± 5.05	0.002
WHR	0.97 ± 0.05	0.94 ± 0.06	0.90 ± 0.17	0.008
Blood glucose, mg/dL	203.68 ± 105.82	173.26 ± 80.31	145.95 ± 43.80	0.033
Urea, mg/dL	28.31 ± 17.09	24.89 ± 8.45	23.33 ± 6.51	0.194
Serum Creatinine, mg/dL	1.01 ± 0.57	0.85 ± 0.32	0.80 ± 0.23	0.064
Hemoglobin (Hb)	13.93 ± 2.45	12.67 ± 2.17	12.84 ± 1.86	0.007
Packed Cell Volume (pcv)	41.23 ± 6.25	37.67 ± 5.40	39.14 ± 4.33	0.004
Total Leukocyte Count (TLC)	12451.37 ± 11540	10443 ± 9552.17	8642.86 ± 1627.75	0.26
CPK	352 (125.75-1636.25)	128 (83-268.25)	-	-
CPK-MB	44.50 (22.25-152.25)	22 (15.25-30.50)	-	-
LVEF (%)	47.42 ± 8.68	57.22 ± 9.66	59.62 ± 10.89	0.0001
RWMA (%)	56 (87.5)	19 (33.3)	5 (23.8)	0.0001
Diabetes (%)	39 (60.9)	29 (50.9)	10 (47.6)	0.414
Hypertension (%)	36 (56.2)	32 (56.1)	10 (47.6)	0.77
Smoking (%)	24 (37.5)	10 (17.5)	3 (14.3)	0.018
Dyslipidemia (%)	11 (17.2)	8 (14)	7 (33.3)	0.14
Renal disease (%)	4 (6.2)	1 (1.80)		0.25
F/h/o premature CVD (%)	7 (10.9)	7 (12.3)	4 (19)	0.63
Sedentary lifestyle (%)	17 (26.6)	11 (19.3)	8 (38.1)	0.23
Angio				
Normal and minimal coronaries (%)	9 (14.1)	17 (29.8)	9 (42.9)	0.036
SVD (%)	27 (42.2)	15 (26.3)	4 (19)	
DVD (%)	16 (25)	11 (19.30)	1 (4.80)	
TVD (%)	11 (17.2)	9 (15.8)	3 (14.3)	
TAC (mM)	1.56 ± 1.01	2.03 ± 1.23	2.55 ± 1.34	0.002
Galectin-3 (ng/ml)	8.73 ± 3.53	8.43 ± 2.64	-	0.61
Soluble ST2 (ng/ml)	50.02 (26.36-89.46)	23.09 (15.67-32.69)	-	0.0001
MMP-9 (ng/ml)	372.97 (144.83-935.71)	172.05 (69.99-389.90)	-	0.005

BMI: Body Mass Index; STEMI: ST-Segment elevation myocardial infarction; NSTEMI: Non–ST-Segment elevation myocardial infarction; WHR: Waist-hip- ratio; LVEF: Left Ventricular Ejection Fraction; RWMA: Regional wall motion abnormalities; F/h/o: Family history of; SVD: Single vessel disease; DVD: Double vessel disease; TVD: Triple vessel disease; TAC: Total Antioxidant Capacity

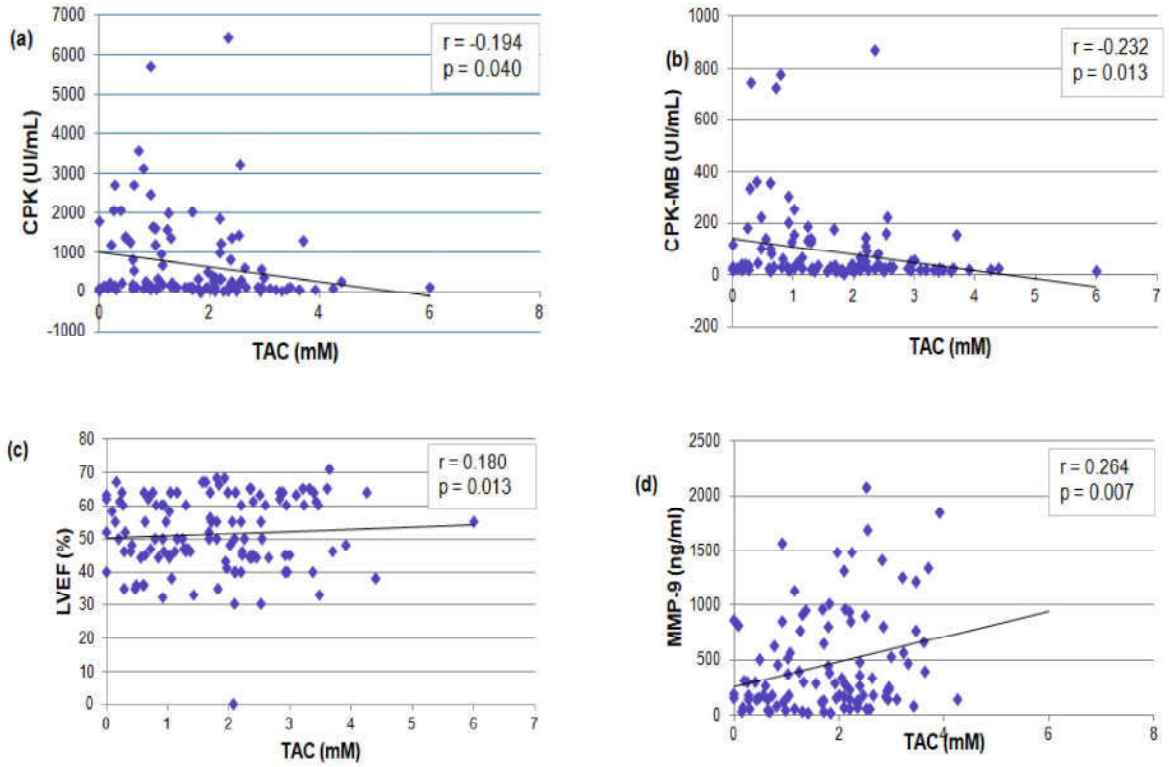
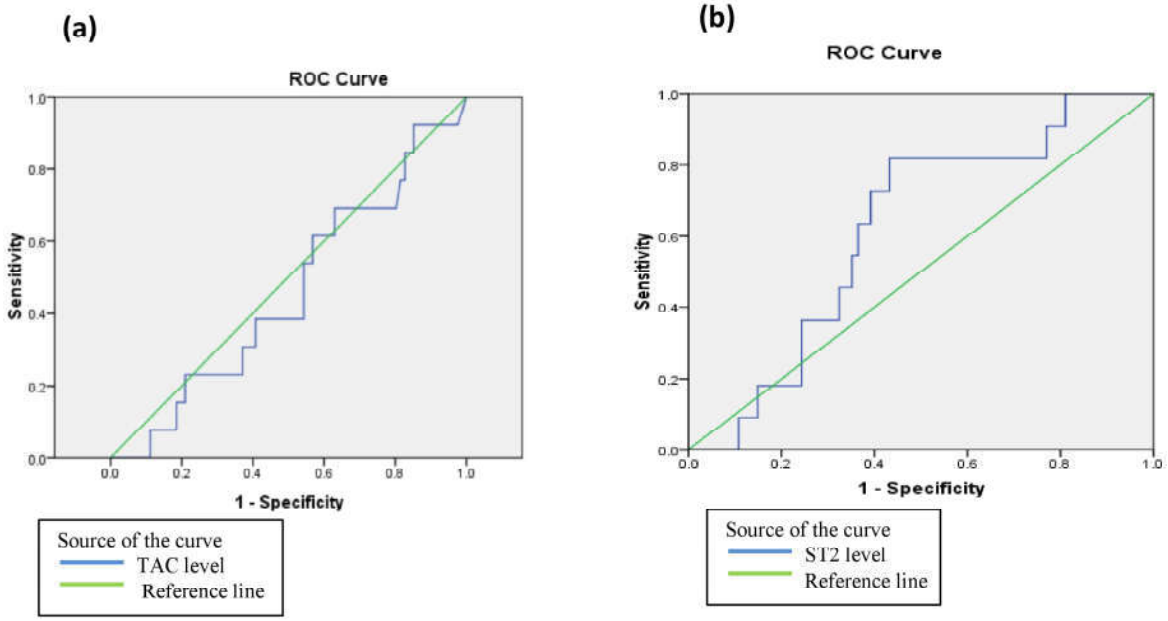


Fig. 2: Correlation between (a) TAC and CPK, (b) TAC and CPK-MB, (c) TAC and LVEF and (d) TAC and MMP-9 levels.



Area Under the Curve

Test Result Variable (s): TAC

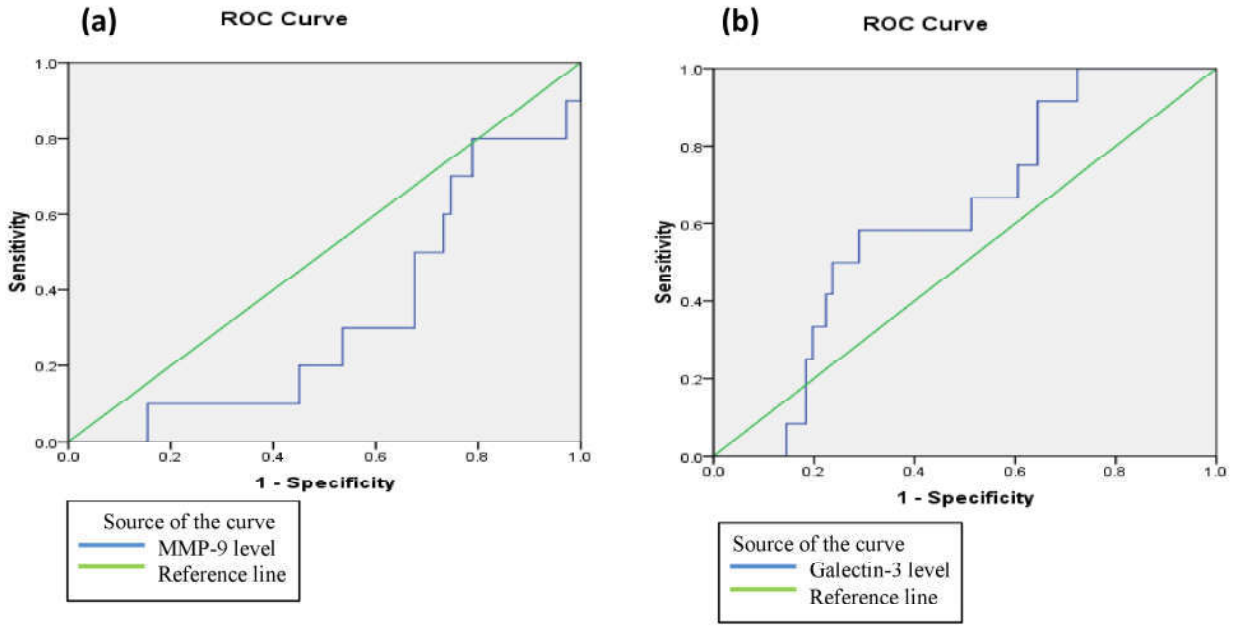
Area	Std. Error*	Asymptotic Sig*	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.458	.082	.630	.297	.619

Area Under the Curve

Test Result Variable (s): ST2

Area	Std. Error*	Asymptotic Sig*	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.619	.077	.204	.468	.770

Fig. 3(A): ROC curve to determine prognostic ability of (a) TAC and (b) ST2 in ACS patients.



Area Under the Curve

Test Result Variable (s): MMP9

Area	Std. Error*	Asymptotic Sig*	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.327	.083	.077	.163	.490

Area Under the Curve

Test Result Variable (s): Gal-3

Area	Std. Error*	Asymptotic Sig*	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.617	.074	.193	.473	.762

Fig. 3(B): ROC curve to determine prognostic ability of (a) MMP-9 and (b) Galectin-3 in ACS patients.

between TAC and other biomarkes: sST2 (r=-0.096, p=0.318) and Galectin-3 (r=0.102, p=0.282). There was significant negative correlation between TAC and CPK and CPK-MB levels (r=-0.194, p=0.040 and r=-0.232, p=0.013; respectively). Correlation between the cardiac biomarkers was also assessed. Correlation was significantly positive between MMP-9 and ST2, MMP-9 and Galectin-3, and ST2 and Galectin-3 (r=0.363, p=0.0001; r=0.391, p=0.0001 and r=0.260, p=0.006, respectively) (Fig. 2).

We followed up the patients at intervals of 3 months, 6 months, 9 months and 12 months after the initial event. The median follow-up period was of 9 months. We observed 13 MACE, of which 8 events were of mortality and 5 were of re-hospitalization due to cardiac events. ROC analysis was done to determine the predictive ability of TAC for MACE for which the AUC was 0.46 [p-value=0.630, 95% CI (0.30-0.62)]. Upon ROC analysis for Galectin-3 for MACE, AUC of 0.56 was obtained [p-value=0.540, 95% CI (0.39-0.73)]. AUC for the predictive ability of sST2 for MACE was 0.63 [p-value=0.220, 95% CI (0.48-0.77)]. AUC for prediction of MACE by MMP-9 was 0.312 [p-value=0.068, 95% CI (0.14-0.49)] (Fig. 3).

Discussion

Oxidative stress is a condition that exists when the level of ROS are elevated compared to the effects of the antioxidative defense mechanisms. ROS are by-products of regular oxygen metabolism which are produced ubiquitously throughout all the cells and aid in homeostasis processes such as cell proliferation, signaling, and apoptosis, gene expression. In this study, we attempted to find the role of TAC levels towards prognostication of ACS patients [10]. We observed the STEMI study group to have the least TAC level, followed by NSTEMI/USA, CSA, and healthy volunteers, respectively. We can assume that lower levels of antioxidant levels may point toward a heightened level of ROS. The present findings are in accordance with several other studies. Bastani et al. found

a significant difference between the TAC levels in CAD and healthy controls with CAD patients having remarkably low TAC compared to healthy volunteers [11]. In another study, Serdar Z et al. found elevated levels of MDA in ACS patients and low levels of antioxidants such as carotenoids, Vitamin E and Vitamin C [12]. Serum MDA levels have been identified to be higher after myocardial infarction [13-14]. Increased levels of ROS with decreased levels of antioxidants have been implicated in the oxidation of lipoproteins which is pro-atherogenic in nature. Oxidation products such as acrolein and α, β–unsaturated aldehydes are known to inactivate Glutathione peroxidase and Thioredoxin/Thioredoxin reductase which are antioxidant enzymes crucial in redox balance in cells. ROS compounds such as Acrolein are also known to modulate the expression of Cox-2 which leads to an increase in Prostaglandin concentration. They also cause an increase in levels of Tumor Necrosis Factor (TNFα), Interleukin-6 (IL-6) and Interleukin-8 (IL-8) causing atherosclerosis, and endothelial injury and inflammation. On the other hand, antioxidants which exist in the body as complex protein systems as well as small molecules, play a role in cellular ROS to less reactive forms, thus maintaining homeostasis. Antioxidant supplements such as α-tocopherol, β-carotene, ascorbic acid are known to reduce carotid atherosclerosis by reducing coronary calcium.

We observed in our study that the male population had low levels of TAC compared to females. Gender is supposed to have an impact on the generation of ROS and regulation of antioxidant systems. In vitro level of oxidative stress has been found to be higher in males compared to females. Also, ROS productions from vascular cells are reported to be elevated in men, unlike women [15]. Estrogen, a prominent female hormone has been known to have antioxidant activities and participate in scavenging free radicals. An important antioxidant enzyme system such as Superoxide Dismutase (SOD) was found to have higher expression in female rats compared to male rats. The expression, however, became similar upon castration in female rats [16]. In a study in age-matched young men and women, levels of Plasma thiobarbituric acid-reactive substances (TBARS) and urinary 8-isoprostaglandin F2alpha (8-iso-PGF2 alpha), oxidative stress markers, were found to be higher in men compared to women [17]. An animal study has also shown that female rats had higher antioxidant capacity than males [18]. These examples highlight the protective mechanisms in place in females for protection against oxidative stress. We also found antioxidant levels to be lower in diabetic patients compared to non-diabetic patients. Diabetes leads to increased production of ROS in the body by non-enzymatic glycation of proteins, glucose oxidation and increased lipid peroxidation which leads to damage of cellular machinery [19]. For example, diabetes leads to increased polyol pathways reflux which oxidizes glucose to fructose in a stepwise manner using NADPH as a co-factor. NAPDH also acts as a co-factor important antioxidant enzyme systems such as GSH. Reduction of NAPDH will make these systems redundant and lower the levels of TAC. Also, patients having diabetes are known to have a poor outcome after an ischemic event and increased risk of heart failure. Increase in ROS in diabetes affects the neovascularization process and normalized tissue survival which leads to poor vasculogenesis in response to ischemia [20]. Our study also found low concentrations of TAC in hypertensive patients. Oxidative stress is known to increase endothelial dysfunction, vascular inflammation and affect structure remodeling which can lead to enhanced peripheral resistance and elevated blood pressure. Studies have found increased plasma H_2O_2 in hypertensive patients. In a study, blood pressure was found to positively and significantly correlate with Myeloperoxidase, which is a known ROS component [21]. Elevated blood pressure has also been found to be negatively correlated with eNOS inhibitor and lipid peroxidation by-products [22]. One study claimed that high free fatty acid (FFA) increases the ROS levels leading to lower eNOS mRNA expression and impaired endothelial-dependent vasodilation (EDV) and elevated blood pressure [23]. These cases highlight the causal relationship between oxidative stress, hypertension, and vascular components. Some studies have also reported a beneficial effect of Vitamin C in rat hypertension model and reduction in blood pressure of hypertensive patients upon intake of a short-term high dose of antioxidants [24].

Galectin-3, a chimeric protein from lectin family is responsible for several immunological functions such as neutrophil activation and adhesion, chemoattraction of monocytes and macrophage activation [25]. All these activities lead to vascular inflammation and plaque destabilization. Post MI, Galectin-3 is also responsible for fibrosis [26]. Galectin-3 was found to downregulate levels of Peroxiredoxin-4 (Prx-4) which is a known antioxidant. Thus, it could be assumed that Galectin-3 reduces TAC and increases the level of oxidative stress markers [27]. Soluble ST2 is a decoy receptor for IL-33 which is known to have

both protective as well as a detrimental role in maintaining oxidative stress levels in cells. One study reported sST2 to negatively correlate with levels of Ceruloplasmin, known to have antioxidant properties, whereas, in another study, it was found to be directly associated with MDA levels and indirectly related to SOD activity [28,29]. Thus, the consensus on the activity of sST2 is unclear. We did not find any correlation between these markers and oxidative stress levels in our study. It could be due to the overall complexity of the entire antioxidant pathway with multiple factors in play and our attempt to assess the relationship between total antioxidant levels with these biomarkers, instead of a few specific ones. MMP-9, a metalloprotease known for its role to degrade extracellular matrix, is known to have role in oxidative stress [30]. However, in a study MMP-9 levels were positively correlated with TAC level which was attributed to the activity of the enzymatic antioxidant systems to compensate the oxidative stress microenvironment being created by MMP-9 [31]. To our knowledge, this is the first study to assess the role of TEAC as a single assay to assess TAC as a prognostic indicator in ACS patients. However, we did not get any positive relationship between their level and occurrence of MACE which might reflect the complex antioxidant – oxidant system and perhaps, a unified global test may get affected by the multitude of pathways. Similar studies have found TAC levels correlating with disease severity, however, they did not identify TAC level to be an independent predictor of CAD event [32,33]. Furthermore, Braun et al. found no association between oxidative stress and adverse outcome in CAD patients after coronary stenting [34]. Future work would be directed towards an increase in sample size along with comparing the efficiency of whole antioxidant status and individual molecules.

Our study involved a heterogeneous group of subjects; however, a small sample size for each group might have restricted detection of statistical associations. Another limitation of the study is that only ACS patients were followed for adverse events. Follow up for CSA patients might have provided detail information. ACS patients were using statins, which are known to have protective antioxidant properties. It is difficult to analyze to what degree use of statins might have affected the results. In addition, plasma TAC levels reflected the concentration of circulating antioxidants and not at the atherosclerotic plaque which is the target tissue in CAD patients.

Conclusion

Plasma TAC levels were significantly higher in patients with ACS compared to CSA and healthy volunteers; however, the TAC level was not able to predict the risk of future adverse events in ACS patients.

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Conflict of Interest: All the authors reviewed and approved the original submitted version of the manuscript

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Presentation at a meeting : Nil

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