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The Relation of Autonomic Biomarkers to the Patient's Outcome with Acute Coronary Syndrome

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Abstract

Objectives: This study aimed to evaluate the neurohormonal activity in patients with acute coronary syndrome and their relation to clinical outcomes by measuring plasma chromogranin A and plasma and RBC cholinesterase activity.

Methods: In this case-control study, cardiac and neurohormonal parameters were compared between fifty-one patients with acute coronary syndrome admitted to the cardiac center in Azadi teaching Hospital in Duhok-Iraq, and thirty comparable gender and age-healthy subjects.

Results: A significant increase in sympathetic activity was reported in patients with the acute coronary syndrome, reflected by the rise in the plasma chromogranin A compared to the control group (994.47 vs. 1203.95 ng/L, respectively, $P < 0.05$). Meanwhile, cardiac troponin was significantly elevated in those patients compared to healthy subjects (0.17 vs. 4.82 ng/ml, respectively). However, the parasympathetic biomarkers (plasma and RBC cholinesterase activity) did not differ substantially between patients and healthy controls (0.83 vs. 0.92, $P > 0.05$ and 1.36 vs. 1.37, $P > 0.05$, respectively). Serum troponin I was more valid than chromogranin A in differentiating acute coronary syndrome from healthy subjects. The area under the curve for troponin I was (0.989) compared to (0.724) for chromogranin A. Furthermore, plasma chromogranin A but not plasma and RBC cholinesterase activity was significantly increased in fatal cases compared to nonfatal patients (1166.68 vs. 3435.64 ng/L).

Conclusion: Plasma chromogranin A was less effective than troponin I in detecting acute coronary cases; however, it can be helpful as a prognostic marker in those patients. Parasympathetic biomarkers were not appreciable in diagnosing and detecting risky patients.

Keywords: Autonomic biomarkers, chromogranin A, plasma and RBC cholinesterase activity, acute coronary syndrome

Introduction

Despite the scientific community's remarkable efforts, cardiovascular diseases account for over one-third of all mortality globally.[1] Furthermore, according to World Health Organization statistics, acute myocardial infarction is the human's most important cause of death.[2]

Acute coronary syndrome (ACS) is the leading cause of death, disability, and human misery worldwide. Unfortunately, their incidence rises with age; however, this happens much earlier in men than in women.[3,4]

ACS is often diagnosed by clinical presentation, electrocardiogram, elevated cardiac enzymes, and echocardiography.[5] In recent years, breakthroughs in the sensitivity and precision of cardiac troponin testing and advances in imaging modalities have helped to diagnose acute chest pain.[6]

Although recent advancements in medical and interventional therapy options have improved the diagnosis and earlier treatment of individuals suffering from ACS, ACS is still one of the world's top causes of morbidity and death. Therefore, identifying the high-risk patient population is crucial in averting such unfavourable scenarios and controlling the aggressiveness of therapeutic options.[7]

In the last decade, it has become apparent that autonomic dysregulation has played a significant role in developing and progressing severe cardiovascular disorders such as myocardial infarction, heart failure, and sudden cardiac death.[8] In addition, cardiac disease can lead to sympathovagal imbalances, which are essential in triggering and maintaining atrial and ventricular cardiac arrhythmias.[9]

Arrhythmias, particularly ventricular arrhythmias, are the primary cause of death in individuals with myocardial infarction. Researchers previously reported that several factors, such as sympathetic neuronal remodelling, gap junction remodelling, and cardiac fibrosis, can establish ventricular arrhythmias following myocardial infarction.[10]

During acute myocardial ischemia, pain, anxiety, and a drop in cardiac output or systemic blood pressure might contribute to increased sympathetic activity and generation of norepinephrine. The secreted norepinephrine stimulates sympathetic nerve regeneration and nerve remodelling, ultimately leading to arrhythmogenesis.[11]

Assessment of cardiovascular autonomic nerves is not straightforward since various variables, like body posture, emotional state, consumed food, and medications, impact autonomic function. Furthermore, no single cardiovascular autonomic test is sufficiently reliable; thus, combining different approaches is necessary.[12]

Chromogranin A measurement has gained interest in cardiovascular disease because increased plasma concentrations are associated with the increased risk of clinical deterioration and death in patients with acute coronary syndromes or chronic heart failure.[13]

Chromogranin A is primarily produced by adrenal medulla cells and adrenergic terminals, although it may be made by myocardial cells under stress conditions. After secretion, it cleaves into several biologically active fragments, including vasostatins and catestatin.[14]

Physiologically chromogranin A is necessary for blood pressure regulation and cardiac inotropic and chronotropic function. In addition, Chromogranin A was a sensitive marker of myocardial dysfunction, with a high predictive value in heart failure and ischemic heart disease clinical outcomes.[15]

In contrast to the sympathetic branch of the autonomic nervous system, the parasympathetic branch has anti-inflammatory effects. Nicotinic receptors stimulation mediates this anti-inflammatory response by reducing the release of inflammatory markers IL 6 and TNF alpha from tissue macrophages.[16] As a result of its link to systemic inflammation, parasympathetic dysfunction may increase the risk of cardiovascular disease.[17] Unfortunately, until now, no clinically reliable test exists for direct measurement of the parasympathetic activity in the body; because acetylcholine is exceptionally labile, and its quantification in circulation is not dependable and unreliable. Furthermore, traditional non-invasive markers of cardiac autonomic dysfunction, such as heart rate variability and blood pressure during exercise recovery, are poor predictors of cardiovascular disease.[18] Therefore, an indirect method of cholinergic activity may be used by measuring serum cholinesterase activities as parasympathetic biomarkers (acetylcholinesterase, butyrylcholinesterase activity, or both).

Disturbances in the levels of AChE have been linked to inflammation and metabolic dysfunction in otherwise healthy adults.[19] However, a study on coronary angiography showed low levels of blood AChE activity in patients who developed significant adverse cardiovascular events over two years of follow-up.[20] Moreover, Serum BChE has been implicated in the development of coronary artery diseases (CAD),[21] demonstrating that individuals in the lowest quintile of BChE activity had significantly higher rates of all-cause and cardiovascular mortality. In addition, Goliasch and a co-worker (2012) showed a strong association between decreased serum cholinesterase and long-term adverse outcomes in patients with known CAD, which was more robust in stable patients with CAD than in those with ACS.[22]

Impaired cardiac parasympathetic responsiveness, enhanced sympathetic activity, and their induced inflammatory responses are negative prognostic indicators for morbidity and mortality associated with arrhythmias and sudden death.[23] Therefore, interventions that reduce sympathetic tone and increase parasympathetic activity may reduce the risk of sudden cardiac death and ventricular tachyarrhythmias. De Ferrari and colleagues observed that weak sympathetic reflexes characterize approximately 75% of animals resistant to ventricular fibrillation in response to acute myocardial ischemia. In the remaining 25%, powerful vagal reflexes counteract concomitant reflex sympathetic hyperactivity, decrease heart rate, and are essential for survival.[24,25]

The study aimed to assess autonomic nervous system activity in patients with acute coronary syndrome by measuring plasma chromogranin A and plasma and RBC cholinesterase activity. In addition, to identify the relationship between autonomic activity and clinical outcomes in patients with the acute coronary syndrome.

Methodology and Study Design

This case-control study was conducted at the Azadi Teaching Hospital in Duhok and College of Pharmacy, University of Duhok, from September 2021 to March 2022. After taking ethical committee approval (24102021-10-32R1), two groups of subjects of both genders, ages 35 and 75 years, were included in this study; however, pregnant women, patients taking cholinesterase antagonists, and patients with chronic inflammatory and neoplastic diseases were excluded from this study. The first group comprised 51 patients with acute coronary syndrome confirmed by a cardiologist and admitted to the cardiac center or cardiac care unit (CCU) within 24 hours of the onset of symptoms. They were recruited sequentially for this study; patients with ACS comprised 34 males and 17 females. The second group consisted of 30 healthy subjects (18 males and 12 females) of comparable age and gender, randomly selected from the Azadi Teaching Hospital staff in Duhok-Iraq.

Data acquired at study entry included age, gender, chief complaint and duration, past medical history, family history, and drug history. In addition, a blood sample was taken from all patients (3 ml of venous blood) within 24 hours from the acute attacks. And the control subjects fasted overnight (10–12 hours). The blood samples were collected in an EDTA tube and, for less than one hour, centrifuged at 3000 (rpm) for 10 min at –4°C. Then the plasma and RBC were separated and deeply frozen at –20°C until the analysis.

Plasma Chromogranin A concentration was measured using Human Chromogranin-A, CGA ELISA Kit, 2021 Shanghai Korean Biotech Co. (Cat No. E1730Hu). While serum troponin I was measured using Cobas®6000 (Cobas e 601) Roche HITACHI, Elecsys Troponin I STAT KIT, Germany. The diagnostic value for ACS in males and females was > 0.3 ng/ml. In addition, plasma and RBC cholinesterase activity were measured using the electrometric method.[26,27]

The statistical calculations were conducted in JMP pro version 14.3.0. The general and medical information of patients and control was introduced in mean and standard deviation (SD), or %, and number. The sympathetic and parasympathetic factor comparisons among patients and healthy subjects were determined in an independent t-test. Comparisons of sympathetic and parasympathetic factors in patients with different characteristics were evaluated in an independent *t*-test or one-way ANOVA. The area under the curve for the acute coronary syndrome diagnosis from healthy controls for Chromogranin A and troponin I level was examined in the ROC curve. The cut-offs were explored from the ROC table and presented in sensitivity and specificity. Statistically, the significance of the difference level was determined by a *P*-value of < 0.05.

Results

This study recruited eighty-one participants. Thirty healthy individuals served as a control group, and fifty-one were patients diagnosed with acute coronary syndrome. The mean age of the participants was 57.06 years (control = 55.06 years vs. patients = 58.53), and nearly two-thirds of the participants were male, 18 (60%) from the control group, and 34 (66.7%) were patients. Statistically, there was no difference between the patient and control group regarding age and gender. More than two-thirds of the patients were diagnosed with STEMI 35 (68.63%), and the others were diagnosed with NSTEMI 16 (31.37%). Meanwhile, around one-third of the patients, 17 patients (33.33%), had a positive family history of ischemic heart diseases. Statistically, there was a highly significant difference among the patients regarding family history of ischemic heart diseases and prevalence of ACS, as shown in Table 1.

Table 2 illustrates the biochemical parameters of the studied participants. These biochemical markers reflect autonomic nervous system activity and cardiac biomarker. In this study, chromogranin A, which reflects the overall sympathetic activity in the blood, was significantly increased in patients with ACS compared to the control group (994.47 vs. 1203.95 ng/L, respectively) Figure 1. In addition, troponin I, which reflects myocardial cell damage, was highly significantly different in ACS patients compared to healthy subjects (0.17 vs. 4.82 ng/ml, respectively) Figure 2. In contrast to the sympathetic system, parasympathetic biomarkers such as plasma and RBC cholinesterase activity did not differ substantially between ACS patients and healthy controls (0.83 vs. 0.92 and 1.36 vs. 1.37, respectively).

Table 3 shows the influence of gender, age, readmission, past medical history, and family history on blood autonomic markers. No statistically significant differences were reported in these biomarkers between males and females as well as among the different age groups of the patients. Similarly, no statistically significant difference in these markers was reported concerning the duration of readmission to the hospital.

However, there was a highly significant increase in the level of plasma chromogranin A in patients with a previous history of ischemic heart disease compared to those who did not have ischemic heart disease (1854.80 VS 1206.12 ng/L). In comparison, there were no statistically significant differences in plasma and RBC cholinesterase ($P > 0.05$). Meanwhile, there was a significant difference in plasma chromogranin A levels between individuals with a family history of myocardial infarction (MI) and those without a family history of MI (1763.52 vs. 1255.32 ng/L). However, there was no statistically significant difference in plasma or RBC cholinesterase levels between the two groups ($P > 0.05$).

Furthermore, patients admitted to the hospital within the first 24 hours from symptoms had a statistically significant lower plasma chromogranin A level (1199.04 VS 1939.63 ng/L) than those admitted after 24 hours. However, there were no statistically significant changes in plasma and RBC cholinesterase activity ($P > 0.05$).

Table 4 demonstrated that patients who had previously taken beta-blockers, statins, or antiplatelets were not statistically different from those who had previously been naive to these medications in terms of plasma concentration of chromogranin A, RBC, and plasma, cholinesterase activity ($P > 0.05$).

Table 1. **Comparisons of general information between patients with acute coronary syndrome and healthy controls**

Participants information	Study groups no (%)		*P*-value (two-sided)
	Control ($n = 30$)	Patients ($n = 51$)	
Age	55.60 (10.66)	58.53 (11.77)	0.2665
Gender			
Male	18 (60.00)	34 (66.67)	0.5456
Female	12 (40.00)	17 (33.33)	
Final diagnosis			
STEMI		35 (68.63)	NA
NSTEMI		16 (31.37)	
History of IHD			
No	30 (100)	34 (66.67)	0.0004
Yes	0 (0.00)	17 (33.33)	

Pearson chi-squared test was performed for statistical analyses.

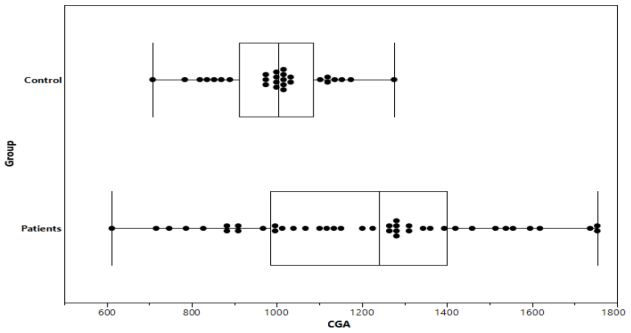

Fig. 1 **Box plot of comparisons of Plasma Chromogranin A between ACS cases and healthy controls.**

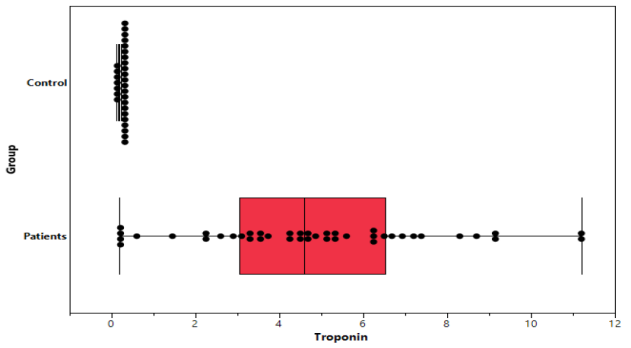

Fig. 2 **Box plot of comparisons of Troponin I between ACS cases and healthy controls.**

Table 2. **Comparisons of autonomic and cardiac biomarkers between patients and healthy controls**

Chemical factors	Study groups Mean (SD)		*P*-value (two-sided)
	Control ($n = 30$)	Patients ($n = 51$)	
Plasma Chromogranin A Range	994.47 (127019) 583.98–1447.27	1203.95 (293.48) 611.69–6970.28	**0.0007**
Plasma Cholinesterase activity Range	0.92 (0.13) 0.27–1.58	0.83 (0.23) 0.35–1.66	**0.1016**
RBC cholinesterase activity Range	1.37 (0.12) 0.81–1.82	1.36 (0.13) 0.03–1.62	**0.7268**
Troponin I	0.17 (0.03)	4.82 (2.81)	**<0.0001**

An independent *t*-test was performed for statistical analyses.

Table 3. **Comparisons of autonomic factors in patients with different characteristics ($n = 51$)**

Characteristics of participants	Sympathetic and parasympathetic factors Mean (SD)		
	Chromogranin A	Plasma cholinesterase	RBC cholinesterase
Gender[a]			
Male	1176.27 (312.43)	0.82 (0.24)	1.35 (0.13)
Female	1265.72 (246.01)	0.86 (0.21)	1.38 (0.14)
P-value	0.3676	0.5227	0.4843
Age category[b]			
36–45	1090.70 (272.77)	0.87 (0.16)	1.40 (0.10)
46–60	1176.45 (283.36)	0.89 (0.27)	1.32 (0.18)
61 and older	1278.74 (305.89)	0.76 (0.18)	1.36 (0.12)
P-value	0.2931	0.1536	0.3931
Past medical history[a]			
IHD	1854.80 (1065.28)	0.83 (0.19)	1.33 (0.12)
No IHD	1206.12 (273.30)	0.84 (0.25)	1.38 (0.14)
P-value	**0.0024**	0.9176	0.1946
Family history[a]			
MI or IHD	1763.52 (1142.59)	0.84 (0.21)	1.35 (0.14)
No MI or IHD	1255.32 (259.69)	0.83 (0.25)	1.37 (0.13
P-value	**0.0324**	0.8769	0.6406
Readmission time[a]			
Within one week	2599.70 (1930.37)	0.91 (0.24)	1.31 (0.15)
Within one month	1248.24 (291.33)	0.79 (0.22)	1.39 (0.12)
Within three months	1256.29 (0.0608)	0.66 (0.3757)	1.57 (0.1431)
P-value			
Admission duration[b]			
Within 24 hrs.	1199.04 (294.98)	0.83 (0.23)	1.35 (0.14)
After 24 hrs.	1939.63 (1095.33)	0.82 (0.27)	1.43 (0.09)
	0.0008	0.8993	0.1943

[a]An independent *t*-test and [b]ANOVA one-way were performed for statistical analyses.

Table 4. **Comparisons of autonomic factors in patients with a drug history**

Drug history	Sympathetic and parasympathetic factors Mean (SD)		
	Chromogranin A	Plasma cholinesterase	RBC cholinesterase
Statin			
No statin	1216.88 (293.81)	0.84 (0.22)	1.36 (0.14)
Statin	1149.04 (305.36)	0.78 (0.27)	1.31 (0.21)
P-value	0.5629	0.4515	0.4086
Antiplatelet			
Not received	1189.23 (274.83)	0.84 (0.25)	1.37 (0.14)
Received	1251.07 (359.12)	0.81 (0.18)	1.34 (0.12)
P-value	0.5673	0.7168	0.5287
Beta-blockers			
Not received	1212.33 (287.78)	0.81 (0.21)	1.34 (0.11)
Received	1180.36 (322.25)	0.91 (0.29)	1.42 (0.17)
P-value	0.7605	0.2068	0.0687

An independent *t*-test was performed for statistical analyses.

Although patients with ST-elevation myocardial infarction (STEMI) showed a lower level of chromogranin A than those with non-ST-elevation myocardial infarction (NSTEMI); however, there was no statistical difference between the two groups. Meanwhile, plasma and RBC cholinesterase activity were also lower in STEMI than in those with NSTEMI; however, this difference was not statistically different between the two groups ($P > 0.05$), as shown in Table 5.

Patients who were readmitted to the hospital after an acute coronary syndrome had higher chromogranin A levels than those who were not (1292.25 (286.95 vs. 1131.01 (284.34, respectively); nonetheless, there was no significant difference between the two groups ($P > 0.05$). However, there was a significant rise in plasma chromogranin A levels in fatal instances (death cases) compared to nonfatal cases (stable patients) (1166.68 vs. 3435.64 ng/L). In contrast, there was no statistically significant difference in plasma and RBC cholinesterase activity between the fatal and nonfatal outcome patients ($P > 0.05$).

The validity parameters of plasma chromogranin A and Troponin I in differentiating ACS from healthy control are shown in Tables 6 and 7. Serum troponin I was of the highest validity in determining ACS from healthy subjects with an area under the curve (AUC) of 0.989 (Figure 3), while chromogranin A was of the lower validity (AUC = 0.724) for differentiating ACS cases from controls (Figure 4).

Table 5. **Comparisons of autonomic factors in patients with diagnosis and clinical outcomes**

Diagnosis and clinical outcomes	Sympathetic and parasympathetic factors Mean (SD)		
	Chromogranin A	Plasma cholinesterase	RBC cholinesterase
Final diagnosis[a]			
NSTEMI	1282.74 (268.43)	0.89 (0.36)	1.39 (0.12)
STEMI	1172.44 (301.40)	0.83 (0.20)	1.33 (0.16)
P-value	0.2765	0.4467	0.2475
Follow-up[a]			
Not admitted	1131.01 (284.34)	0.84 (0.24)	1.35 (0.13)
Readmitted	1292.25 (286.95)	0.82 (0.22)	1.38 (0.13)
P-value	0.0760	0.7301	0.4312
Patient outcome[a]			
Died	3435.64 (2552.09)	0.73 (0.17)	1.37 (0.15)
Stable	1166.68 (285.83)	0.84 (0.23)	1.36 (0.13)
P-value	**<0.0001**	0.1969	0.7918

[a]An independent *t*-test and [b]ANOVA one-way were performed for statistical analyses.

Table 6. **ROC area for plasma chromogranin A (ng/L) in differentiating ACS cases from healthy controls**

	Prob	Specificity (%)	Sensitivity (%)			PPV (%)	NPV (%)	Accuracy (%)
1038.915	0.6507	96.43	52.38			95.7	57.4	70.00
1032.583	0.6479	96.43	54.76	Optimum	*	95.8	58.7	71.43
1021.419	0.6448	92.86	54.76			92.0	57.8	70.00
1019.573	0.6421	92.86	57.14			92.3	59.1	71.43
1017.321	0.6419	89.29	57.14			88.9	58.1	70.00
1016.976	0.6398	89.29	59.52			89.3	59.5	71.43

The cut-off is between 1016.976 and 1038.915 for the diagnosis of acute coronary syndrome. Therefore, the optimum concentration for diagnosing acute coronary syndrome is 1032.58.

Table 7. **ROC area for Troponin I (ng/ml) in differentiating ACS cases from healthy controls**

	Prob	Specificity	Sensitivity	Sens-(1-Spec)		PPV	NPV	Accuracy
0.6000000	1	100.00	90.48	0.9048		100.0	87.9	94.37
0.2400000	0.6856	100.00	92.86	0.9286	*	100.0	90.6	95.77
0.2300000	0.55	93.10	92.86	0.8596		95.1	90.0	92.96
0.2200000	0.4064	93.10	95.24	0.8834		95.2	93.1	94.37
0.2100000	0.2773	89.66	95.24	0.8489		93.0	92.9	92.96
0.2000000	0.1769	82.76	97.62	0.8038		89.1	96.0	91.55
0.1900000	0.1075	72.41	100	0.7241		84.0	100.0	88.73
0.1800000	0.0632	58.62	100	0.5862		77.8	100.0	83.10

The cut-off is between 0.18 and 0.6 for the diagnosis of acute coronary syndrome. (The optimum number for the diagnosis of the acute coronary syndrome is 0.24).

Regarding plasma chromogranin A, the cut-off value was between 1016.976 and 1038.915 for the diagnosis of the acute coronary syndrome. The optimum number for the diagnosis of the acute coronary syndrome is 1016.976 (Table 6). Regarding serum troponin I, the cut-off value was between 0.18 and 0.6 for the diagnosis of the acute coronary syndrome. The optimum number for the diagnosis of the acute coronary syndrome is 0.24 (Table 7).

Discussion

Acute coronary syndrome (ACS) primarily affects patients over the age of 50 years. However, younger patients can also be concerned with a higher prevalence of STEMI, even with less severe coronary artery disease.[28] The average age of the ACS patient in this study was 58.53 years which is nearly similar to another study done in Duhok city.[29] Huffman and colleagues reported 60.6 years as the mean age for ACS patients in their study conducted in India.[30] However, in the Global Registry of Acute Coronary Events (GRACE) across 14 countries, the mean age of patients with STEMI was 64 years, NSTEMI was 68 years, and unstable angina was 66 years. This disparity in the mean age of ACS patients between low and high-income countries probably reflects socio-economic burdens, unhealthy lifestyles, and poor health education in low and medium-income countries.[31]

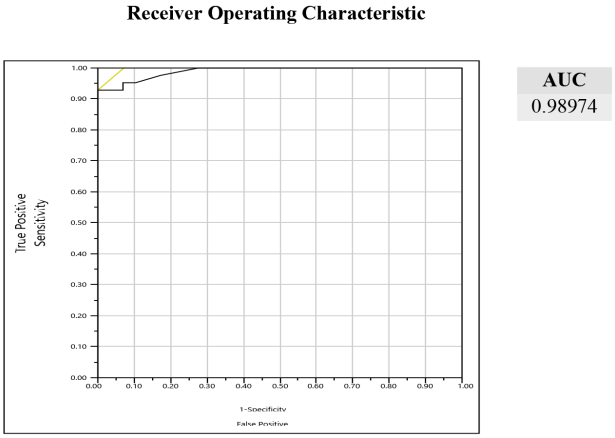

Fig. 3 **ROC curve showing the trade-off between sensitivity (true positive) and 1- specificity (false positive) for Troponin I when used in differentiating ACS patients from healthy controls.**

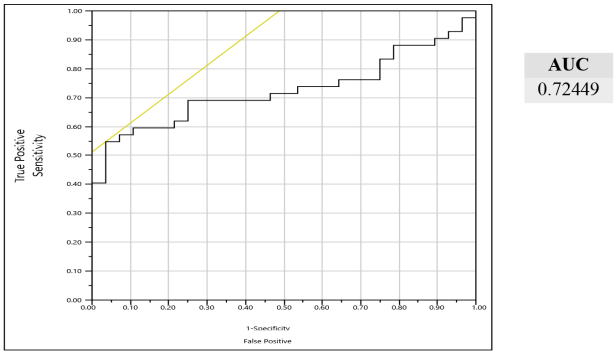

Fig. 4 **ROC curve showing the trade-off between sensitivity (true positive) and 1- specificity (false positive) for plasma chromogranin A when used in differentiating ACS patients from healthy controls.**

The prevalence of STEMI and NSTEMI varies in different studies conducted on ACS cases; some researchers reported a higher prevalence of NSTEMI than STEMI among their studied individuals.[32,33] In this study, however, more than two-thirds of the patients (68.63%) were diagnosed with STEMI, similar to Ricci and co-workers (2017), who reported a higher prevalence of STEMI in their survey, particularly in younger patients, which contradict the previous studies done by Bhatt and co-workers and others. The higher prevalence of STEMI among study participants could be attributed to gender, with males being affected more than females. Furthermore, at younger ages, males were more susceptible to STEMI than females.[34]

The family history of IHD is a non-modifiable long-term independent risk factor for ACS. It represents a genetic predisposition to coronary artery disease, particularly in younger people.[35] This observation was evident in a study conducted in Pakistan, where researchers looked for risk factors for ACS in patients aged 18 to 40; nearly one-third of their participants had a positive family history of IHD.[36] In concordance with that study, almost two-thirds of the participants recruited in this study had a positive family history of IHD. Webring and co-workers (2016) also reported that CAS more frequently occurred in patients with a positive family history of ischemic heart disease.[37]

In recent years, high-sensitivity cardiac troponin (hs-cTn) assays have emerged as the preferred biomarker in the universal definition of myocardial infarction. It dramatically helped to diagnose acute chest pain. This study also confirms cardiac troponin's role in diagnosing ACS. A dramatically higher troponin level was observed in the blood in almost all cases of ACS compared to the control group. Furthermore, elevated cardiac troponins levels have been linked to poor outcomes in ACS in elderly patients.[38] However, the predictive value of cardiac troponin is not absolute for all cases of ACS. For example, high-risk patients with unstable angina usually do not have cardiac troponin elevation.

Furthermore, cardiac troponin levels do not account for all pathological processes associated with ACS, such as left ventricular (LV) dysfunction, hemodynamic stress, inflammation, or renal dysfunction.[39]

Several studies have found that measuring chromogranin A in the blood can reflect sympathetic activity in the body.[40-42]

As a result, this study employs plasma chromogranin A levels to assess sympathetic activation following ACS. Chromogranin A is preferred over other modalities in evaluating adrenergic activity because of its long half-life in the plasma.[43]

The potential role of chromogranin A as a cardiac biomarker is not an innovative topic. For more than ten years, scientific committees have observed that an increase in the concentration of chromogranin A and its metabolites in the circulation are associated with the risk of clinical worsening and death in patients with acute coronary syndromes or chronic heart failure.[13,44,45] Angelone and colleagues (2012) reported a high plasma chromogranin A level in patients with acute coronary syndromes.[43,46] This elevation correlates with conventional cardiovascular biomarkers such as BNP and endothelin-1 (ET-1).[47] Ji and colleagues (2012) also reported that catestatin, a chromogranin A metabolite, is an independent predictor of in-hospital complications in STEMI patients like heart failure and malignant arrhythmia.

Furthermore, patients with angina had significantly higher plasma catestatin levels than those who did not have IHD.[48] Others, however, are skeptical of the significance of chromogranin A as a prognostic indicator of ACS and heart failure. This biological molecule, they believe, is not a specific cardiac biomarker, and its elevation can be seen in chronic inflammatory diseases, autoimmune diseases, renal failure, and hepatic insufficiency.[49]

Similar to the finding of Angelone and colleagues, this study also showed a significantly increased plasma chromogranin A in patients with ACS compared to normal individuals. Qasim and colleagues reported a similar finding in patients with acute myocardial infarction in Duhok, Iraq.[50] This study also reported a higher plasma level of chromogranin A in patients with a history of IHD and a positive family history of IHD, which contradicts the study by Qasim and co-workers. The elevation in plasma chromogranin A level in patients with ACS is not unexpected, given that its release increases under stress conditions like ACS cases.[51] And their metabolites are generated by proteolytic processing in the heart to protect the heart from ischemia/reperfusion damage through inhibiting cardiac contraction and relaxation, counter-regulating beta-adrenergic, and endothelinrgic stimulation.[46,47]

Furthermore, this study also reported that patients who were delayed for more than 24 hours to the point of definitive care had significantly higher plasma chromogranin A levels.

This elevation could be due to the release of chromogranin A from the myocardium after a prolonged ischemic period.[52] In addition, chromogranin A levels have risen in proportion to clinical severity and are associated with prognosis in patients with chronic and post-infarction heart failure. As a result, the level of chromogranin A in the blood may indicate the degree of cardiac damage.[53]

Meanwhile, vasostatin I, a derivative of chromogranin A, showed an antiadrenergic activity in the heart.[54]

After three months of follow-up of all cases of ACS, nearly 17% of patients have died. A higher level of chromogranin A was reported in those fatal cases compared to nonfatal ones, and the difference was statistically significant.[43] Anna and co-workers also reported that circulating chromogranin A levels would be predictive of the incidence of death in ACS.[43] Meanwhile, high chromogranin A levels predict mortality in severely septic patients without prior cardiovascular disease.[55]

Furthermore, D'amico and colleagues reported that high chromogranin A plasma levels are strictly associated with the risk of mortality after myocardial infarction or acute coronary syndrome, as well as heart failure.[56]

Although there were some differences between plasma and RBC cholinesterase activity; however, no statistically significant difference was reported in these enzymes between the ACS cases and the healthy control group in this study, as well as among patients with ACS. However, a noticeable reduction in plasma but not RBC cholinesterase activity was observed among patients. This reduction was primarily seen in STEMI cases, patients not taking statin lipid-lowering drugs, and unstable patients who required readmission to the hospital, especially after one and three months; meanwhile, it was reported in fatal cases. Ackland and co-workers found that parasympathetic dysfunction may increase the risk of cardiovascular disease. This association was related to immunological dysregulation induced by cholinergic dysfunction.[17] Arbel and colleagues also reported a low level of blood AChE activity in cases of coronary angiography who developed significant adverse cardiovascular events over two years of follow-up.[20] Calderon and co-workers also noticed that low serum levels of BChE have been linked to a higher cardiovascular mortality rate.[21] However, Goliasch and co-workers demonstrated a strong association between low serum cholinesterase activity and long-term adverse outcomes in stable cases of coronary artery diseases.[22]

Conclusion

Plasma chromogranin A was less effective than troponin I in detecting acute coronary cases; however, it can be helpful as a prognostic marker in those patients. The role of parasympathetic biomarkers was not appreciable in the early diagnosis and detection of risky patients with acute coronary syndrome. ■

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