Integrated Oxidative and Cardiac Biomarker Profile in Type 2 Diabetes Mellitus With Acute Coronary Syndrome

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Abstract- Type 2 diabetes mellitus (T2DM) substantially increases the risk of acute coronary syndrome (ACS) through the combined effects of chronic hyperglycemia, dyslipidemia, oxidative stress, endothelial dysfunction, and myocardial injury. This study aimed to comprehensively evaluate metabolic, oxidative stress, and cardiac biomarkers in patients with T2DM complicated by ACS, and to investigate their diagnostic performance and interrelationships. A case-control study was conducted including 60 patients with T2DM complicated by ACS and 30 apparently healthy controls. Fasting blood glucose (FBS), glycated hemoglobin (HbA1c), lipid profile, glutathione, lipid peroxidation, superoxide, homocysteine (HCY), Na+/K±ATPase, and cardiac troponin were determined using standard laboratory methods. Compared with healthy controls, patients with T2DM and ACS exhibited significantly elevated FBS, HbA1c, total cholesterol (TC), triglycerides, low-density lipoprotein cholesterol (LDL-C), very-low-density lipoprotein cholesterol (VLDL-C), HCY, and lipid peroxidation, whereas high-density lipoprotein cholesterol (HDL-C), glutathione, and Na+/K±ATPase activity were significantly reduced (all $P<0.001$). Superoxide levels were also significantly decreased in patients compared with healthy controls ($P<0.001$). Correlation analysis demonstrated a significant positive correlation between cardiac troponin and Na+/K±ATPase activity (r=0.337, $P=0.008$), while no significant correlations were observed between FBS, HbA1c, lipid profile parameters, oxidative stress biomarkers, HCY, and the remaining investigated biomarkers. ROC analysis demonstrated excellent diagnostic performance for Na+/K±ATPase, glutathione, lipid peroxidation, superoxide, and HCY, with high sensitivity and specificity for discriminating patients from healthy controls. In conclusion, patients with T2DM complicated by ACS exhibit profound metabolic disturbances coupled with pronounced oxidative stress, hyperhomocysteinemia, altered Na+/K±ATPase activity, and myocardial damage, highlighting the utility of integrated biomarker profiling.
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Introduction

Type 2 diabetes mellitus is a chronic, progressive disease influenced by a multifaceted interaction of genetic, physiological, and behavioral factors (1). Cardiovascular disease is the leading cause of morbidity and mortality among diabetic individuals, with a markedly higher incidence compared to non-diabetics. Patients with T2DM develop accelerated atherosclerosis at an earlier age, characterized by larger, more vulnerable plaques and narrower coronary arterial lumens than non-diabetic individuals (2). Moreover, diabetic dyslipidemia, characterized by increased triglycerides and atherogenic lipoprotein levels with decreased HDL-C cholesterol, exacerbates plaque development and instability, thereby leading to acute coronary incidents (3). Diabetic patients have a two- to four-fold higher risk of coronary artery disease, myocardial infarction, heart failure, and stroke compared with non-diabetic individuals (4).

The excess cardiovascular risk in T2DM arises from

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a complex interplay between insulin resistance, chronic hyperglycemia, oxidative stress, dyslipidemia, inflammation, endothelial dysfunction, and accelerated atherosclerosis (5). Chronic elevation of glucose stimulates various interconnected biochemical pathways, such as the polyol pathway, activation of protein kinase C, hexosamine biosynthetic pathway, the synthesis of advanced glycation end-products, and oxidative stress. These mechanisms hasten cardiovascular damage through oxidative injury, endothelial impairment, inflammation, and detrimental cardiac remodelling (6).

The association between metabolic dysfunction and cardiovascular complications among patients with T2DM might occur through increased reactive oxygen species and impaired antioxidant defence mechanisms, which contribute to several complications, including lipid peroxidation, endothelial dysfunction, reduction of nitric oxide bioavailability, and structural myocardial damage. Subsequently, oxidative stress biomarkers may provide more detailed data beyond conventional glycemic and lipid parameters when assessing cardiovascular risk in diabetic patients (7,8).

In addition, other biochemical markers such as HCY, Na+/K+-ATPase activity, and cardiac injury biomarkers, particularly cardiac troponin, emerged as promising biomarkers to improve cardiovascular risk stratification in patients with T2DM. Therefore, integrating conventional metabolic indices, oxidative stress biomarkers, and cardiac molecular markers may provide a more comprehensive identification of disease severity and prediction of cardiovascular complications than depending on single biomarkers alone (9,10). Unfortunately, few studies have comprehensively investigated these biomarkers simultaneously in patients with T2DM complicated by ACS. Therefore, this study aimed to perform an integrated profiling of metabolic, oxidative, and cardiac biomarkers to elucidate their combined clinical utility in patients with T2DM complicated by ACS.

Materials and Methods

Study Design

This hospital-based case-control study was conducted at the Educational Laboratories, Medical City, Baghdad, Iraq, between January and June 2026. The study was approved by the Scientific and Ethics Committee of the College of Health and Medical Technologies, Middle Technical University. Written informed consent was obtained from all participants before enrollment. Individuals with autoimmune diseases, chronic liver disease, malignancy, severe renal disease, acute infectious diseases, and pregnant women were excluded from the study.

Subjects and Sample Size

This study included 90 participants in two groups: the control group, which included 30 apparently healthy participants and the case group, comprising 60 patients diagnosed with T2DM complicated by ACS. The larger patient group was selected to increase the statistical power for correlation and diagnostic performance analyses. The diagnosis of T2DM and ACS was established by consultant physicians according to standard clinical and laboratory criteria.

Blood sample collection

Venous blood specimens were obtained from all subjects after an overnight fast in accordance with conventional aseptic protocols. Blood specimens were allowed to coagulate, and serum was isolated by centrifugation at 3000 rpm for a duration of 10 minutes. Serum aliquots were preserved at −80° C until biochemical assessment.

Methods

Serum concentrations of HCY, Na+/K+-ATPase, total glutathione, superoxide radical, lipid peroxidation markers (malondialdehyde), and cardiac troponin were measured using commercial enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturers' instructions.

Fasting blood sugar (FBS), glycated haemoglobin (HbA1c), total cholesterol (TC), triglycerides (TG), HDL-C, LDL-C, and VLDL-C were measured using an automated clinical chemistry analyzer CS-T180 Automated Chemistry Analyzer (DIRUI Industrial Co., China). All assays were performed according to the manufacturers' protocols

Statistical analysis

Statistical analysis was performed using SPSS software version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean±standard deviation (SD). Comparisons between patients and controls were performed using the independent samples Student's t-test. Pearson's correlation coefficient was used to evaluate the relationships among the investigated biomarkers. ROC curve analysis was performed to determine the diagnostic performance of the studied biomarkers. A two-tailed $P<0.05$ was considered statistically significant.

Results

A total of 90 participants were enrolled in the present study, including 60 patients with T2DM complicated by ACS and 30 apparently healthy controls. No statistically significant differences were observed between the case and control groups regarding age (*P*=0.099) or sex distribution (*P*=0.230), as shown in Table 1.

The mean levels of FBS, HbA1C, and cardiac troponin were statistically significantly higher in the case group compared to the control group (*P*=0.001 for all), as displayed in Table 2.

The mean values of TG, TC, and LDL-C were significantly higher in the case group compared to the control group (213.67±84.3 versus 126.43±17.6 mg/dl, 219.63±60.7 versus 160.17±12.5 mg/dl, and 115.46±35.2 versus 91.10±7.4 mg/dl, respectively, P-values=0.001 for all) while the mean value of HDL-C was significantly lower in the case group compared to the control group (45.92±13.3 versus 81.57±17.3 mg/dl, *P*=0.001). The mean values of lipid peroxidation and HCY were significantly higher in the case group compared to the control group (6.04±1.5 versus 1.25±0.5 and 1718.85±353.5 versus 398.67±92.2, respectively, P-values=0.001 for both). The mean values of Na+/K+ATPase, glutathione, and superoxide were significantly lower in the case group compared to the control group (0.80±0.1 versus 3.06±1.9, 5.88±1.3 versus 18.94±5.8, and 1.24±0.5 versus 5.23±1.0, respectively, *P*=0.001 for all), as shown in Table 3.

In the case group, there was a significant positive correlation between the troponin level and Na+/K+ATPase level (Pearson Correlation=0.337; *P*=0.008). In contrast, there were no significant correlations between lipid profile, FBS, HbA1C, and troponin level with glutathione, lipid peroxidation, superoxide, and HCY (Table 4 and Table 5).

The ROC curve was used to estimate the cut-off points of Na K ATPase, glutathione, lipid peroxidation, superoxide, and HCY with the best sensitivity and specificity in the diagnosis of DM and ACS. The cut-off point of glutathione was ≤8.178 with sensitivity and specificity of 98.3 and 96.7, respectively. The cut-off point of Na K ATPase was ≤1.101 with sensitivity and specificity of 100% for both. The cut-off point of superoxide was ≤2.859 with sensitivity and specificity of 100% for both. The cut-off point of lipid peroxidation was >2.807 with sensitivity and specificity of 100% for both. The cut-off point of HCY was >597.726 with sensitivity and specificity of 100% for both. As shown in Figure 1.

According to multivariate binary logistic regression, the studied variables were not significant independent factors that affected the incidence of ACS among T2DM patients (Table 6).

Table 1. Distribution of age and sex according to the study groups

Group studies		Case groups N(%)	Control group N(%)	P-value
Age (years)	<40	18(30.0)	16(53.3)	0.099
	40-49	20(33.3)	7(23.3)	
	50-59	9(15.0)	5(16.7)	
	≥60	13(21.7)	2(6.7)	
Sex	Male	52(86.7)	23(76.7)	0.230
	Female	8(13.3)	7(23.3)	

Table 2. Distribution of FBS, HbA1C, and cardiac troponin according to the study groups

Parameters	Case groups Mean±SD	Control group Mean±SD	*P*
FBS (mg/dl)	193.17±38.0	102.27±11.36	0.001
HbA1C (mg/dl)	10.97±10.6	5.20±0.2	0.001
Cardiac troponin (mg/dl)	758.31±997.2	0.03±0.009	0.001

Table 3. Distribution of lipid profile, Na+/ K+ -ATPase, glutathione, lipid peroxidation, superoxide, and HCY according to the study groups

Parameters	Case groups Mean±SD	Control group Mean±SD	P-value
TG (mg/dl)	213.67±84.3	126.43±17.6	0.001
TC (mg/dl)	219.63±60.7	160.17±12.5	0.001
HDL-C (mg/dl)	45.92±13.3	81.57±17.3	0.001
LDL-C (mg/dl)	115.46±35.2	91.10±7.4	0.001
Na+/K⁺ -ATPase	0.80±0.1	3.06±1.9	0.001
Glutathione	5.88±1.3	18.94±5.8	0.001
Lipid peroxidation	6.04±1.5	1.25±0.5	0.001
Superoxide	1.24±0.5	5.23±1.0	0.001
HCY	1718.85±353.5	398.67±92.2	0.001

Table 4. Correlations between FBS, HbA1C, and troponin levels with the studied markers in the case group

		FBS (mg\dl)	HbA1C (%)	Troponin (ng/ml)
Na+/ K+ ATPase	Pearson Correlation	-0.238	0.033	0.337*
	P	0.067	0.805	0.008
	N	60	60	60
Glutathione	Pearson Correlation	0.005	-0.163	0.104
	P	0.968	0.213	0.430
	N	60	60	60
Lipid peroxidation	Pearson Correlation	-0.072	0.077	-0.014
	P	0.584	0.558	0.915
	N	60	60	60
Superoxide	Pearson Correlation	-0.074	-0.076	0.156
	P	0.576	0.562	0.235
	N	60	60	60
HCY	Pearson Correlation	-0.017	-0.102	0.057
	P	0.896	0.437	0.663
	N	60	60	60

*P is significant at a value of <0.05

Table 5. Correlations between TG, TC, HDL-C, and LDL-C levels with Na⁺ /K⁺ -ATPase, glutathione, lipid peroxidation, superoxide, and HCY

		TG (mg\dl)	TC (mg/dl)	HDL-C (mg/dl)	LDL-C (mg\dl)
Na+/K⁺ -ATPase	Pearson Correlation	-0.145	-0.188	-0.123	-0.166
	P	0.269	0.150	0.349	0.206
	N	60	60	60	60
Glutathione	Pearson Correlation	-0.030	-0.251	-0.021	-0.240
	P	0.820	0.053	0.875	0.064
	N	60	60	60	60
Lipid peroxidation	Pearson Correlation	-0.048	0.044	0.121	0.143
	P	0.718	0.737	0.357	0.275
	N	60	60	60	60
Superoxide	Pearson Correlation	-0.199	-0.136	0.057	-0.182
	P	0.128	0.300	0.667	0.165
	N	60	60	60	60
HCY	Pearson Correlation	-0.136	-0.040	-0.122	-0.251
	P	0.301	0.761	0.352	0.053
	N	60	60	60	60

Table 6. Multivariate binary logistic regression

	B	S.E.	Wald	df	Sig.	Exp(B)
Agefroup	-0.319	5632.263	0.000	1	1.000	0.727
Sex.ACS(1)	-4.740	14919.695	0.000	1	1.000	0.009
FBS (Mg\dl)	-0.004	248.969	0.000	1	1.000	0.996
HbA1c %	-2.100	4440.610	0.000	1	1.000	0.122
Troponin ng/ml	-0.001	20.805	0.000	1	1.000	0.999
TG (mg\dl)	-0.007	117.749	0.000	1	1.000	0.993

Cont. table 6

TC (mg/dl)	-0.027	104.245	0.000	1	1.000	0.974
HDL (MG/DL)	0.047	281.268	0.000	1	1.000	1.048
LDL (MG\DL)	0.078	233.902	0.000	1	1.000	1.081
Glutathione	0.180	1401.139	0.000	1	1.000	1.197
Lipid peroxidation	-1.701	5391.706	0.000	1	1.000	0.182
Superoxide	3.194	6530.660	0.000	1	1.000	24.379
HCY	-0.011	31.131	0.000	1	1.000	0.989
Constant	20.582	71524.062	0.000	1	1.000	868503619

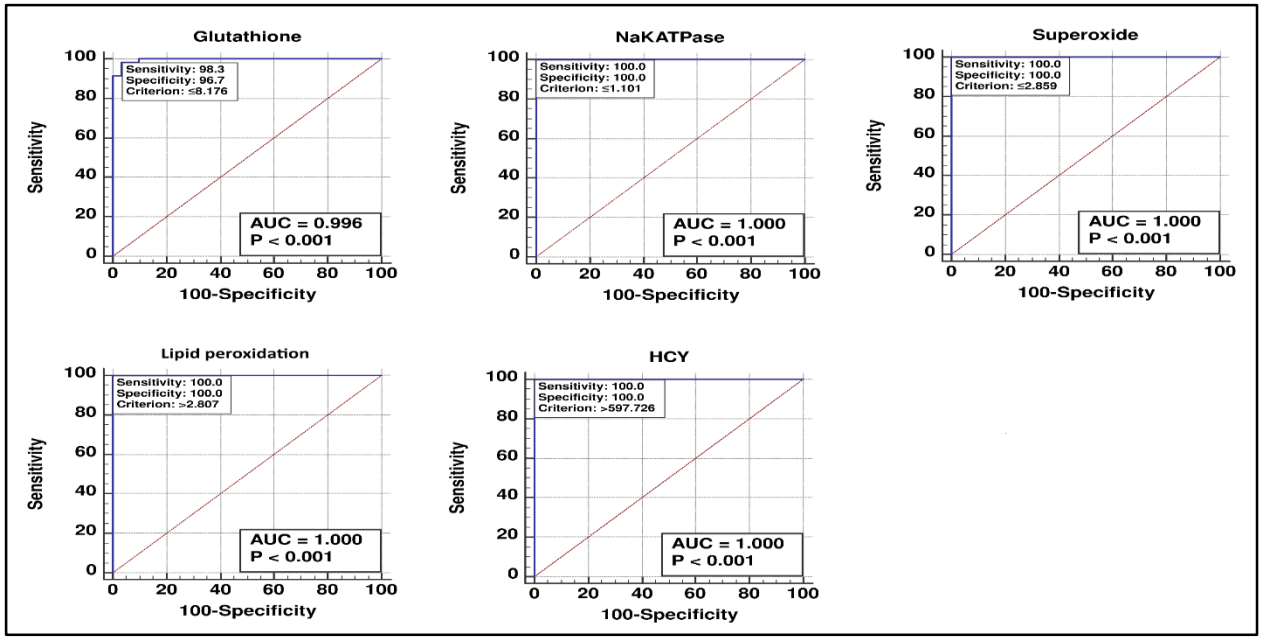

Figure 1. ROC test for the studied markers

Discussion

These findings indicate that both groups were comparable with respect to their baseline demographic characteristics, thereby reducing the likelihood that age- or sex-related differences influenced the biochemical outcomes observed in the present study. Age and sex are well-recognized determinants of cardiovascular risk in patients with T2DM. However, recent evidence suggests that although advancing age increases the absolute incidence of cardiovascular disease, the excess cardiovascular risk associated with diabetes persists even after adjustment for age and sex because metabolic dysfunction and chronic vascular injury are considered major contributors to disease progression. Therefore, ensuring comparable age and sex distributions between study groups is essential for improving the internal validity of biomarker-based clinical investigations (11,12). Sex-related differences in cardiovascular disease among individuals with diabetes have also attracted considerable attention in recent years. Although men generally develop coronary artery disease at an earlier age, women with T2DM frequently experience a greater relative increase in cardiovascular risk compared with women without diabetes, thereby attenuating the traditional sex-related differences in cardiovascular outcomes. Nevertheless, because no significant difference in sex distribution was observed between the present study groups, the influence of sex on the measured biomarkers is expected to be minimal (12,13).

In the current study, lipid profiles, oxidative and antioxidant biomarkers, HCY concentrations, and Na+/K+-ATPase activity exhibited marked dysregulation in patients with T2DM complicated by ACS relative to healthy controls. These findings indicate that metabolic and molecular abnormalities coexist and contribute to vascular injury in patients who had diabetes and an accompanying ACS. Recent studies have highlighted those cardiovascular complications in diabetes result from the interaction of several factors rather than from hyperglycaemia alone (14,15).

In the current study, diabetic patients had

dyslipidaemia in the form of abnormal cholesterol, triglycerides, LDL-C, VLDL-C, and HDL-C. This might be attributed to the fact that insulin resistance promotes hepatic overproduction of VLDL-C, increases the formation of LDL-C, and impairs HDL-C metabolism, leading to accelerated progression of cardiovascular diseases (15,16).

The present study revealed a significant increase in lipid peroxidation and a significant depletion of glutathione, which indicate an imbalance between oxidant production and antioxidant defence. In agreement with these findings, other studies concluded that oxidative stress biomarkers can be considered as valuable indicators for cardiovascular risk assessment among diabetic patients. The proposed mechanism is that persistent hyperglycaemia enhances reactive oxygen species generation through mitochondrial dysfunction, activation of NADPH oxidase, and advanced glycation end-product formation, leading to endothelial dysfunction and progression of atherosclerosis, and finally, myocardial injury (17,18).

The patients in the current study had hyperhomocysteinaemia compared to healthy participants. Current suggestions indicate that elevated HCY contributes to cardiovascular disease oxidative stress amplification and its complications, leading to accelerated atherosclerotic progression (19,20).

The significant reduction in Na^+/K^+-ATPase activity among patients compared to healthy participants was another important finding of the present study. Na^+/K^+-ATPase is recognized as an important signalling molecule involved in regulating oxidative stress, calcium homeostasis, inflammatory conditions, and cardiomyocyte survival. In therapy, any oxidative modification of membrane lipids and proteins may impair enzyme activity, leading to electrical instability and myocardial dysfunction (21,22).

The correlation analysis performed in the present study demonstrated a significant positive association between cardiac troponin and Na+/K+-ATPase activity in patients with T2DM complicated by ACS, whereas no significant correlations were observed between glycemic parameters (FBS and HbA1c) and the remaining investigated biomarkers. These findings suggest that myocardial injury occurring during ACS may be more closely associated with alterations in membrane ion transport than with the degree of glycemic control or the oxidative stress biomarkers measured in the present study. Recent evidence indicates that myocardial injury in diabetic patients is a multifactorial process involving disturbances in membrane signalling, mitochondrial function, and cardiomyocyte integrity in addition to metabolic abnormalities, thereby supporting the observed association between cardiac troponin and Na+/K+-ATPase activity (21,22).

The significant positive association between cardiac troponin and Na+/K+-ATPase activity may reflect the important role of this membrane enzyme in maintaining myocardial cellular homeostasis during ischemic injury. The Na+/K+-ATPase maintains intracellular sodium and potassium gradients, but there is increasing evidence that indicates it can serve as a signalling platform that regulates several biological mechanisms, including intracellular calcium balance, oxidative stress, inflammatory pathways, mitochondrial stability, and cardiomyocyte viability. Diminished Na+/K+-ATPase performance may therefore lead to electrical instability, impaired contractility, and ongoing myocardial damage. This might explain its correlation with increased circulating cardiac troponin levels in individuals with ACS (21,23).

In contrast, FBS and HbA1c showed no significant correlations with glutathione, lipid peroxidation, superoxide, or HCY. Although chronic hyperglycaemia is widely accepted as a major initiator of oxidative stress in diabetes, recent investigations indicate that oxidative injury in patients with established cardiovascular disease is influenced by several interacting mechanisms, including persistent inflammation, endothelial dysfunction, mitochondrial damage, duration of diabetes, pharmacological therapy, and individual biological variability rather than glycaemic status alone. Consequently, the absence of significant correlations in the present study does not exclude the contribution of hyperglycaemia to oxidative injury but rather reflects the multifactorial pathophysiology of oxidative stress in patients with T2DM complicated by ACS (16,18).

Among patients in the case group, the lack of significant correlations between cardiac troponin and glutathione, lipid peroxidation, superoxide, or HCY suggests that these oxidative disturbances reflect background chronic metabolic distress rather than the acute extent of myocardial necrosis per se. The oxidative stress biomarkers are particularly valuable for assessing long-term cardiovascular risk and disease progression, while troponin is a sensitive and specific biomarker for detecting acute myocardial injury (24,25). The correlation analysis performed in the present study demonstrated no significant associations between serum lipid profile parameters (TG, TC, HDL-C, and LDL-C) and Na^+/K^+-ATPase activity, glutathione, lipid peroxidation, superoxide, or HCY in patients with T2DM

complicated by ACS. Similar results have been reported in other studies (14,16). These findings suggest dyslipidaemia, oxidative stress, and membrane dysfunction represent interconnected yet relatively independent pathophysiological processes rather than exhibiting direct linear relationships in diabetic cardiovascular disease.

Na^+ /K^+ -ATPase activity was not significantly correlated with any lipid profile parameters. Cumulative clinical and experimental evidence indicates that oxidative modification of membrane phospholipids, intracellular calcium overload, mitochondrial dysfunction, and inflammatory cascades—rather than circulating lipid levels—serve as primary drivers of suppressed Na+/K+-ATPase activity (21,23). Based on these findings, it seems that systemic lipid abnormalities are less of a reflection of cellular damage and oxidative damage than membrane ion transport problems (21,23).

The absence of significant correlations between serum lipid parameters and HCY is also consistent with current evidence indicating that hyperhomocysteinaemia represents an independent cardiovascular risk factor. Elevated HCY contributes to inflammation, endothelial dysfunction, oxidative stress, vascular damage, and thrombus formation through mechanisms that are largely independent of conventional lipid metabolism. Therefore, dyslipidaemia and hyperhomocysteinaemia are likely to exert complementary rather than directly correlated effects on cardiovascular risk in patients with T2DM complicated by ACS (19,26).

The ROC curve analysis performed in the present study demonstrated excellent diagnostic performance for Na^+ /K^+ -ATPase, glutathione, lipid peroxidation, superoxide, and HCY in distinguishing patients with T2DM complicated by ACS from healthy controls. The remarkably high sensitivity and specificity observed for these biomarkers indicate their potential. When evaluating cardiovascular illness, recent studies have shown that using a combination of biomarkers that reflect diverse pathophysiological pathways is more accurate and thorough than using a single biomarker alone (27,28).

The Na^+ /K^+ -ATPase achieved 100% sensitivity and specificity at the identified cut-off value. This finding suggests that alterations in membrane ion transport may represent a sensitive indicator of myocardial injury in patients with T2DM complicated by ACS. These results agree with other results, which concluded that Na^+ /K^+ -ATPase can be considered a novel biomarker for cardiovascular disease (21,23).

Glutathione, lipid peroxidation, and superoxide also demonstrated excellent diagnostic performance. These results reinforce the role of oxidative stress in the pathogenesis of diabetes-associated cardiovascular disease. Contemporary evidence indicates that oxidative stress biomarkers not only reflect the degree of cellular injury but also improve diagnostic performance when interpreted together with conventional biochemical and cardiovascular markers. Therefore, integrating oxidative stress biomarkers into multimarker strategies may offer a more thorough assessment of disease severity and cardiovascular risk (16,17).

The HCY likewise demonstrated excellent diagnostic performance in the present study. Growing evidence indicates that hyperhomocysteinaemia contributes to endothelial dysfunction, vascular inflammation, oxidative stress, thrombogenesis, and accelerated atherosclerosis, thereby increasing the risk of acute coronary events. Consequently, HCY may assist as a valuable adjunctive biomarker for cardiovascular risk assessment, particularly when evaluated together with oxidative stress biomarkers and established cardiac biomarkers in patients with T2DM complicated by ACS (19,20).

Despite the current findings exhibiting very high sensitivity and specificity, these results must be approached with caution due to the research being performed at a single site with a rather small sample size. Therefore, external validation in larger multicenter prospective studies is required before these biomarkers can be recommended for routine clinical application. Nevertheless, the excellent ROC performance observed in the present study supports the growing concept that integrating metabolic, oxidative stress, membrane-associated, and cardiovascular biomarkers may substantially improve cardiovascular risk stratification and facilitate earlier identification of high-risk patients with T2DM complicated by ACS (14,27,28).

Patients with T2DM complicated by ACS exhibit profound metabolic abnormalities accompanied by severe oxidative stress, hyperhomocysteinemia, impaired Na+/K+-ATPase activity, and increased myocardial injury. The positive association between troponin and Na+/K+-ATPase suggests a potential relationship between altered membrane ion transport and myocardial damage. Collectively, these findings demonstrate the coexistence of metabolic dysregulation, oxidative stress, impaired membrane enzyme activity, and myocardial injury, highlighting the multifactorial pathophysiology of ACS in patients with T2DM. Furthermore, the excellent diagnostic performance of Na+/K+-ATPase, HCY, and oxidative stress biomarkers supports a possible mechanistic association between altered membrane ion

transport and myocardial injury in patients with T2DM complicated by ACS. Larger, multicenter prospective investigations are warranted to externally validate these cutoff values and assess the clinical utility of integrated multi-marker risk assessment strategies.

References

1. Davies MJ, Lim S, Slater T, Goldney J, Philis-Tsimikas A, Franco DR, et al. Type 2 diabetes mellitus. Nat Rev Dis Prim 2026;12:13.
2. Pantea Stoian A, Roman G. Cardiovascular Risk/Disease in Type 2 Diabetes Mellitus. In: Pantea Stoian A, editor. Type 2 Diabetes - From Pathophysiology to Cyber Systems. London: IntechOpen; 2021.
3. Strikić D, Vujević A, Perica D, Leskovar D, Paponja K, Pećin I, et al. Importance of Dyslipidaemia Treatment in Individuals with Type 2 Diabetes Mellitus—A Narrative Review. Diabetology 2023;4:538-52.
4. Marx N, Federici M, Schütt K, Müller-Wieland D, Ajjan RA, Antunes MJ. 2023 ESC Guidelines for the Management of Cardiovascular Disease in Patients with Diabetes. Eur Heart J 2023;44:4043-140.
5. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, et al. Pathophysiology of Type 2 Diabetes Mellitus. Int J Mol Sci 2020;21.
6. Hussain A. Chronic hyperglycemia and cardiovascular dysfunction: an in-depth exploration of metabolic and cellular pathways in type 2 diabetes mellitus. Cardiovasc Diabetol Endocrinol Rep 2025;11:39.
7. González P, Lozano P, Ros G, Solano F. Hyperglycemia and Oxidative Stress: An Integral, Updated and Critical Overview of Their Metabolic Interconnections. Int J Mol Sci 2023;24:9352.
8. Hudspeth B, PharmD C. The burden of cardiovascular disease in patients with diabetes. Am J Manag Care 2018;24:S268-S272.
9. Djuric D, Bajic Z, Radisavljevic N, Sobot T, Mutavdzin Krneta S, Stankovic S, et al. High-Sensitivity Troponins and Homocysteine: Combined Biomarkers for Better Prediction of Cardiovascular Events. Int J Mol Sci 2025;26.
10. Mou L, Fu Z, Wang TB, Chen Y, Luo Z, Wang X, et al. Na+/K±ATPase: a multifunctional target in type 2 diabetes and pancreatic islets. Front Immunol 2025;16:1555310.
11. Wong ND, Sattar N. Cardiovascular risk in diabetes mellitus: epidemiology, assessment and prevention. Nat Rev Cardiol 2023;20:685-95.
12. LeBlanc ES, Brooks N, Davies M, Chatterjee R. Sex-Specific Cardiovascular Risk Factors and Treatment in Females With T2DM and CVD: Developments and Knowledge Gaps. J Clin Endocrinol Metab 2024;109:e2167-77.
13. Al-Salameh A, El bouzegaoui N, Saraval-Gross M. Diabetes and cardiovascular risk according to sex: An overview of epidemiological data from the early Framingham reports to the cardiovascular outcomes trials. Ann Endocrinol 2023;84:57-68.
14. Khan AW, Jandeleit-Dahm KA. Atherosclerosis in diabetes mellitus: novel mechanisms and mechanism-based therapeutic approaches. Nat Rev Cardiol 2025;22:482-96.
15. Béliard S, Mourre F, Valéro R. Hyperlipidaemia in diabetes: are there particular considerations for next-generation therapies? Diabetologia 2024;67:974-84.
16. Sabitha S, Hegde SV, Agarwal SV, Delna N, Pillai A, Shah SN, et al. Biomarkers of oxidative stress and their clinical relevance in type 2 diabetes mellitus patients: a systematic review. Cureus 2024;16.
17. Li X, Zou J, Lin A, Chi J, Hao H, Chen H, et al. Oxidative stress, endothelial dysfunction, and N-acetylcysteine in type 2 diabetes mellitus. Antioxid Redox Signal 2024;40:968-89.
18. Rajlic S, Treede H, Münzel T, Daiber A, Duerr GD. Early detection is the best prevention—characterization of oxidative stress in diabetes mellitus and its consequences on the cardiovascular system. Cells 2023;12:583.
19. Unadkat SV, Padhi BK, Bhongir AV, Gandhi AP, Shamim MA, Dahiya N, et al. Association between homocysteine and coronary artery disease—trend over time and across the regions: a systematic review and meta-analysis. Egypt Heart J 2024;76:29.
20. Mokgalaboni K, Mashaba GR, Phoswa WN, Lebelo SL. Folic acid supplementation on inflammation and homocysteine in type 2 diabetes mellitus: systematic review and meta-analysis of randomized controlled trials. Nutr Diabetes 2024;14:22.
21. Dhalla NS, Elimban V, Adameova AD. Role of Na±K+ ATPase alterations in the development of heart failure. Int J Mol Sci 2024;25:10807.
22. Elezaby A, Lin AJ, Vijayan V, Pokhrel S, Kraemer BR, Bechara LR, et al. Cardiac troponin I directly binds and inhibits mitochondrial ATP synthase with a noncanonical role in the post-ischemic heart. Nat Cardiovasc Res 2024;3:987-1002.
23. Contreras RG, Torres-Carrillo A, Flores-Maldonado C, Shoshani L, Ponce A. Na+/K±ATPase: more than an electrogenic pump. Int J Mol Sci 2024;25:6122
24. McEvoy JW, Mangan C. Predicting Incident CVD Risk With High-Sensitivity Cardiac Troponin: Mainstream, Niche, or Neither? Washington DC: American College of Cardiology Foundation; 2024

25. Li J, Pan L, Pan W, Li N, Tang B. Recent progress of oxidative stress associated biomarker detection. Chem Commun 2023;59:7361-74.
26. Luciani L, Pedrelli M, Parini P. Modification of lipoprotein metabolism and function driving atherogenesis in diabetes. Atherosclerosis 2024;394:117545
27. Lee DY. Emerging circulating biomarkers for enhanced cardiovascular risk prediction. J Lipid Atheroscler 2024;13:262-79
28. Wilson M, Al- Hamid A, Abbas I, Birkett J, Khan I, Harper M, et al. Identification of diagnostic biomarkers used in the diagnosis of cardiovascular diseases and diabetes mellitus: A systematic review of quantitative studies. Diabetes Obes Metab 2024;26:3009-19.