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Sirtuin-1 in Egyptian patients with coronary artery disease

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Abstract

Background: Coronary artery disease (CAD) represents the leading cause of death worldwide. Animal and human studies have demonstrated that silent information regulator 1 (SIRT1) is involved in a wide range of physiological and pathological processes. This study aimed to measure the plasma level of SIRT1 in patients with CAD and explore its correlation with cardiovascular risk factors.

Results: Plasma SIRT1 was significantly lower in patients with chronic coronary syndrome (CCS) than in those in the control group and was significantly lower in patients with both acute myocardial infarction and unstable angina than in those in the control group and with CCS. Moreover, plasma SIRT1 was positively correlated with platelet count and negatively correlated with cholesterol and triglyceride levels.

Conclusions: The plasma level of SIRT1 is lower in patients with CAD compared to control and it could be a possible marker for this disease. Multi-center studies with follow-up measurements are recommended for further investigation.

Keywords: Atherosclerosis, Coronary heart disease, Sirtuin

1 Background

Coronary artery disease (CAD) involves chronic coronary syndrome (CCS) and acute coronary syndrome (ACS). ACS includes unstable angina (UA) and acute myocardial infarction (AMI). Most cases of ACS arise from the disruption of a previously non-severe lesion (an atherosclerotic lesion that was previously hemodynamically insignificant yet vulnerable to rupture). The vulnerable plaque is made of a large lipid pool, numerous inflammatory cells, and a thin fibrous cap [1].

The pathogenesis of ACS has been attributed primarily to atherosclerosis. The physical crack of the atherosclerotic plaque that develops in patients with ACS represents practically almost all cases of acute coronary thrombi [2].

It was found that caloric restriction, resveratrol, and ischemic preconditioning can protect against ischemic injury to the heart [3]. The underlying mechanisms of these interventions appear to be under the control of a nicotinamide adenine dinucleotide (NAD)-dependent histone deacetylase named silent information regulator 1 (SIRT1) [4]. SIRT1 is a member of the class III group of histone deacetylases, collectively called sirtuins. The mammalian sirtuin family consists of seven members designated SIRT1 through SIRT7.

SIRT1 engages in a wide scope of physiological and pathological processes [5]. However, data on sirtuins in human cardiovascular diseases (CVD) are scant [6]. These proteins assume significant functions in guaranteeing cardiovascular homeostasis under physiological and stress conditions [7] and can influence cardiac and endothelial cells either directly or indirectly by systemic regulation [8].

A recent study found that SIRT1 inhibition causes oxidative stress and inflammation in patients with CAD, whereas its activation reverses these atherosclerotic

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events [9]. The results of this study may provide new knowledge for the management of CAD patients. However, the expression and activity of SIRT1 must be strictly controlled [10].

Several previous studies have assessed plasma SIRT1 levels in patients with CAD. However, there is still a controversy in results. Doulamis et al. [11] stated that SIRT1 has a protective role in advanced CAD and reported low values [11]. On the other side, Kızıltunç et al. [12] found that serum SIRT 1, 3, and 6 levels in AMI patients were similar to those in normal coronary patients. This study denied the possible protective effects of SIRT 1, 3, and 6 in AMI patients.

Another study reported a significant inverse correlation between circulatory SIRT1 and epicardial fat thickness, which is a useful marker of the severity of CAD [13]. Interestingly, a study reported that cardiomyocyte-specific deletion of the *SIRT1* gene sensitizes the myocardium to ischemia and reperfusion injury [14]. Animal and human studies have demonstrated that SIRT1 has a credible protective function in myocardial ischemic injury [15].

In our study, we aimed to measure the plasma level of SIRT1 in CAD patients, assess its potential role as a candidate biomarker for predicting the risk of CAD, and explore the correlation between SIRT1 and cardiovascular risk factors.

2 Methods

This is a case–control study that was carried out at the Internal Medicine and Medical Biochemistry and Molecular Biology Departments. It included 80 individuals divided into the following two groups: Group I (controls), 40 normal individuals; Group II (40 cases), subdivided into Group IIa (CAD with CCS [12 individuals]), Group IIb (CAD with unstable angina (UA) [14 individuals]), and Group IIc (AMI [14 individuals]).

Written informed consent was obtained from the patients or their relatives with an explanation of the study procedure and possible associated hazards. The study was approved by the Institute Review Board.

We included patients with spontaneous ACS or CCS aged between 40 and 60 years admitted through the outpatient and emergency departments. We excluded patients with ACS that had undergone a previous intervention (percutaneous coronary intervention or coronary artery bypass grafting), and patients with any of the following: significant valvular heart disease, hematological disease, malignancy, liver or renal disease, systemic inflammatory disease, active infection, autoimmune disease, and cardiogenic shock. We also excluded patients on steroids (whatever the indication), patients with high total cholesterol levels (above 200 mg/dL), current and former smokers, and obese individuals (body mass index of 30 or higher).

All individuals were subjected to full history taking and physical examination. Peripheral venous blood samples were collected within 24 h of admission for complete blood count (CBC), random blood glucose (RBG), renal function testing, creatine kinase-MB (CK-MB), lipid profile, and SIRT1 measurements. CBC testing was performed using an automated hematology analyzer (BeneSphera, the Netherlands). Serum creatinine and urea, lipid profiles, CK-MB and RBG were measured using a spectrophotometer (Sunostik, Changchun, China). The reagents were provided by (Spinreact, Spain). The plasma SIRT1 level was measured using an enzyme-linked immunosorbent assay (Wuhan Boster Biological Technology Ltd, Wuhan, People's Republic of China).

2.1 Statistical analysis

All data were collected, tabulated, and statistically analyzed using SPSS 19.0 for Windows (SPSS Inc., Chicago, IL, USA) and MedCalc 13 for Windows (MedCalc Software BVBA, Ostend, Belgium). Continuous data were presented as the mean ± standard deviation (SD) and categorical data were presented as frequencies and percentages. We used the Shapiro–Wilk test to check continuous variables for normality. The independent Student *t* test was used to compare two groups of normally distributed data. To compare two groups of non-normally distributed data, we used the Mann–Whitney *U* test, and to compare more than two groups of non-normally distributed data, we used the Kruskal–Wallis test. Percentages of categorical variables were compared using the Chi-square (χ^2) test. Correlations between variables were assessed using the Pearson correlation coefficient. A $p < 0.05$ was considered statistically significant and $p < 0.001$ was considered highly statistically significant.

3 Results

There was no significant difference in age, sex, hemoglobin, RBG, or serum creatinine levels between the study groups ($p = 0.081$, 0.45, 0.74, 0.477and 0.054 respectively). WBCs, platelet count, urea, and BUN differed significantly between the study groups ($p < 0.001$ for each). In the AMI group, platelet count, WBC count, urea, BUN, and CK-MB were significantly higher and platelet count was significantly lower than in the other groups ($p < 0.05$). (Table 1).

Regarding the lipid profile, total cholesterol, TG, and LDL were significantly lower and HDL was significantly higher in the control group than in the other groups ($p < 0.001$) (Table 1).

There was a significant difference in CK-MB levels between the study groups ($p < 0.001$), and it was

Table 1 Demographic and biochemical data of the studied groups

	Control	CCS	Unstable angina	AMI	*p*
Age (years)	51.45 ± 5.32	53.5 ± 6.25	54.71 ± 4.27	57.14 ± 4.01	0.081
Sex (M/F)	11/9	2/4	2/5	2/5	0.45
Hemoglobin (gm/dL)	13.52 ± 1.93	14.21 ± 2.08	14.32 ± 1.81	13.61 ± 1.97	0.74
PLT (cells × 10^3/uL)	264.05 ± 80.29	239.5 ± 71.57	237.14 ± 59.64	92.85 ± 16.03©℗∞	0.001**
WBCs (cells × 10^3/uL)	6.62 ± 2.41	8.25 ± 2.21	7.41 ± 2.25	12.7 ± 1.68©℗∞	< 0.001**
Cholesterol (mg/dL)	125.2 ± 15.98	189.5 ± 7.17©	171.42 ± 19.3©℗	188.57 ± 11.07©∞	< 0.001**
TG (mg/dL)	71.9 ± 22.74	136 ± 12.08©	140.14 ± 8.41©	144 ± 4.86©	< 0.001**
HDL (mg/dL)	61 ± 12.35	38.66 ± 7.03©	37.57 ± 7.36©	32.14 ± 5.66©	< 0.001**
LDL (mg/dL)	83.6 ± 25.14	122.5 ± 15.59©	129.85 ± 11.18©	133.57 ± 10.69©	< 0.001**
RBS (mg/dL)	117.1 ± 17.56	127.33 ± 12.32	124.57 ± 13.4	122.57 ± 15.95	0.477
Urea (mg/dL)	11.65 ± 5.03	11.66 ± 2.16	14.14 ± 3.89	21.42 ± 2.57©℗∞	< 0.001**
Blood Urea Nitrogen (mg/dL)	6.05 ± 2.12	6.16 ± 1.16	7.14 ± 1.95	10.71 ± 1.49©℗∞	< 0.001**
Creatinine (mg/dL)	0.83 ± 0.18	0.98 ± 0.14	0.9 ± 0.19	1.04 ± 0.15	0.054
CK-MB (ug/L)	8.9 ± 1.01	3.83 ± 1.28©	20.57 ± 8.25©℗	187.42 ± 11.16©℗∞	< 0.001**
SIRT1(ng/mL)	5.99 ± 6.23	3.77 ± 5.62©	1.01 ± 1.58©℗	1.03 ± 1.52131©℗	0.04*

CCS: chronic coronary syndrome; UA: unstable angina; AMI: acute myocardial infarction; PLT: platelet count; WBCs: white blood cells; TG: triglycerides; HDL: high-density lipoprotein; LDL: low-density lipoprotein; RBS: random blood sugar; CK-MB: creatine kinase-MB; SIRT1: sirtuin1; *: $p < 0.05$: statistically significant; **: $p < 0.001$: highly statistically significant; ©: significant difference with control; ℗: significant difference with CCC; ∞: significant difference with UA

significantly higher in the CAD groups. There was a significant difference in the plasma level of SIRT1 between the study groups ($p = 0.04$). The plasma SIRT1 level was significantly lower in patients with CCS than in patients in the control group, and was significantly lower in patients with either AMI or UA than in patients of the control and CCS groups ($p < 0.05$), with no significant difference found between patients with AMI and UA ($p > 0.05$) (Table 1).

There was a significant positive correlation between plasma SIRT1 and platelet count ($r = 0.333$, $p = 0.036$) and a significant negative correlation between plasma SIRT1 and both cholesterol ($r = -0.367$, $p = 0.02$) and TG ($r = -0.474$, $p = 0.002$) (Table 2).

There was a significant association and agreement between SIRT1 (at cutoff level < 2.4) and CAD in general ($p = 0.049$) (Table 3). Regarding the receiver operating characteristics (ROC) curve, the plasma cutoff level of SIRT1 in CAD patients was 65.0% accurate in predicting CAD with a significant area under the curve ($p = 0.013$) at a cutoff value of less than 2.4 ng/mL with a sensitivity of 75.0%, specificity of 55.0%, positive predictive value (PPV) of 62.5%, and negative predictive value (NPV) of 68.7% (Tables 4, 5, Fig. 1).

The plasma level of SIRT1 in UA or AMI patients was 60.0% accurate in predicting UA or AMI with a significant area under the curve ($p = 0.014$) at a cutoff value of less than 0.66 ng/mL with a sensitivity of 64.3%, specificity of 57.7%, PPV of 45.5%, and NPV of 75.0% (Tables 6, 7, Fig. 2).

4 Discussion

CVD are still the leading cause of death worldwide. Inflammation plays a substantial role in the initiation and propagation of the atherosclerotic process [16]. Coronary artery luminal obstructions and plaque cracks due to atherosclerosis are the most frequent causes of CAD [17]. Apoptosis and necrosis of cardiomyocytes, endothelial cells, and monocytes with severe

Table 2 Correlations between Sirtuin1 and other studied parameters:

	r	*p*
Age (years)	− 0.309	0.052
Hemoglobin (g/dL)	− 0.222	0.169
WBCs (10^3/uL)	− 0.093	0.569
PLT (10^3/uL)	0.333	0.036*
RBS (mg/dL)	0.073	0.656
Urea (mg/dL)	− 0.117	0.474
Blood Urea Nitrogen (mg/dL)	− 0.068	0.675
Creatinine (mg/dL)	− 0.152	0.348
Cholesterol (mg/dL)	− 0.367	0.02*
TG (mg/dL)	− 0.474	0.002*
LDL (mg/dL)	− 0.250	0.120
HDL (mg/dL)	0.287	0.073
CK-MB (ug/L)	− 0.282	0.077

WBCs: white blood cells; PLT: platelet count; RBS: random blood sugar; TG: triglycerides; HDL: high-density lipoprotein; LDL: low-density lipoprotein; CK-MB: creatine kinase-MB

*: $p < 0.05$ statistically significant

Table 3 Association and agreement between Sirtuin1 cutoff levels and coronary artery disease

	Group		Total	X^2	*p*	Kappa agreement
	Control	CAD				
SIRT1 (ng/mL) cutoff						
> 2.4						
N	22	10	32	3.75	0.049*	0.32
%	59.3%	29.6%	44.4%			
< 2.4						
N	18	30	48			
%	40.7%	70.4%	55.6%			
Total						
N	40	40	80			
%	100.0%	100.0%	100.0%			

*: $p < 0.05$ statistically significant

Table 4 Receiver operating characteristics (ROC) curve for prediction of coronary artery disease. Area under curve (AUC) of sirtuin1 regarding coronary artery disease:

Area under curve (AUC)	Cutoff	*p*	95% Confidence interval	
			Lower bound	Upper bound
0.729	< 2.4	0.013*	0.573	0.884

*: $p < 0.05$ statistically significant

Table 5 Validity of sirtuin 1 for prediction of coronary artery disease

	Sensitivity	Specificity	+VE predictive	-VE predictive	Accuracy
Sirtuin1 cutoff	75.0%	55.0%	62.5%	68.7%	65.0%

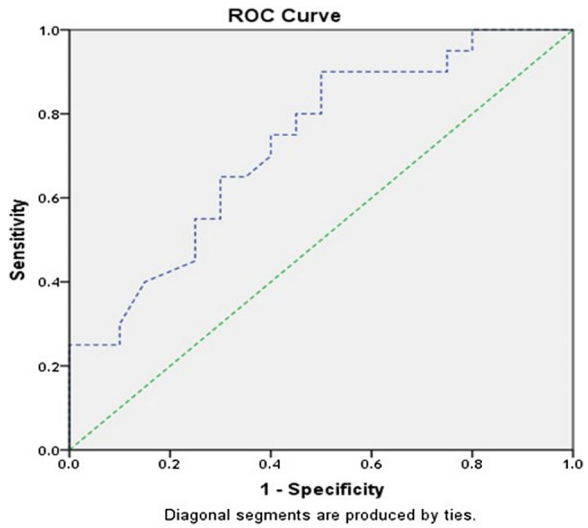

Fig. 1 Receiver operating characteristics (ROC) curve for prediction of coronary artery disease. Significant area under the curve (0.729, $p = 0.013$) with a cutoff of < 2.4 ng/mL, sensitivity 75.0%, specificity 55.0%

Table 6 Receiver operating characteristics (ROC) curve for sirtuin 1 cutoff level in prediction of unstable angina and AMI

Area under curve (AUC)	Cutoff	*p*	95% Confidence interval	
			Lower bound	Upper bound
0.738	< 0.66	0.014*	0.583	0.892

*: $p < 0.05$: statistically significant

inflammation are the major causes of vessel damage under CAD. Thus, strategies that repress cell death and manage unsuitable proinflammatory responses are potential therapeutic strategies for improving the clinical prognosis of patients with CAD [18].

SIRTs are NAD^+-dependent histone deacetylases that are implicated in a variety of cellular functions, including cell cycle regulation and cellular metabolism. Among the seven known human sirtuins, SIRT1 is implicated in a wide range of cellular functions [19].

Baur et al. [20] proposed a role of SIRT1 in aging and diseases that involve ischemia/reperfusion and neurodegeneration [20]. Hsu et al. [21] showed that cardiac-specific knockout *SIRT1* mice exhibit a significant increment in the size of the risky myocardial infarction area [21]. The authors concluded that SIRT1 has a cardioprotective effect. SIRT1 induces the upregulation of cardioprotective molecules and downregulation of proapoptotic molecules, thereby attenuating oxidative stress,

Table 7 Validity of sirtuin1 in prediction of patients with AMI or unstable angina

	Sensitivity	Specificity	PPV	NPV	Accuracy
Sirtuin1 level cutoff	64.3%	57.7%	45.0%	75.0%	60.0%

PPV: positive predictive value; NPV: negative predictive value

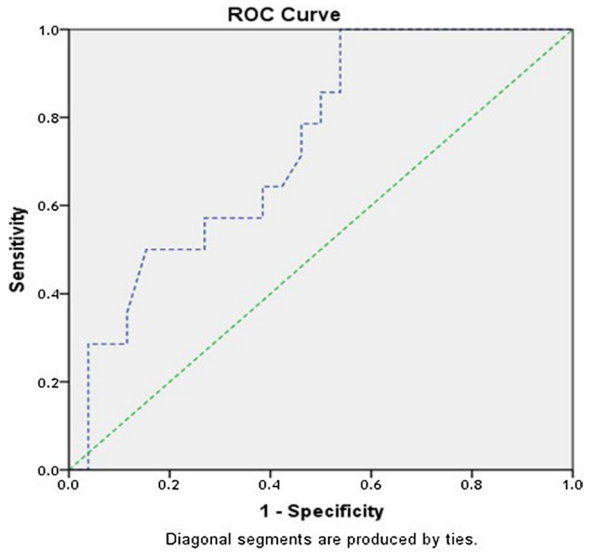

Fig. 2 Receiver operating characteristics (ROC) curve for prediction of unstable angina or acute myocardial infarction. Significant area under the curve (0.738, $p = 0.014$) with cutoff of < 0.66 ng/mL, sensitivity 64.3%, specificity 57.7%

and inhibiting apoptosis. Consequently, the activation of SIRT1 could be a novel method of cardioprotection.

In addition, SIRT1 inhibition causes oxidative stress and inflammation in patients with CAD, whereas the activation of SIRT1 function reverses these atherosclerotic events which may provide new knowledge that is relevant for the management of CAD patients [9].

Stein and Matter [22] demonstrated that SIRT1 delays the progression of atherosclerosis by preventing macrophage foam cell formation [22].

Breitenstein et al. [23] also found that the SIRT1 expression in monocytes was lower in ACS patients. SIRT1 exerts atheroprotective effects on the vascularity by downregulating the expression of various proinflammatory cytokines and mediating vasodilatation via the actions of eNOS-derived nitric oxide and scavenging reactive oxygen species [23].

To our knowledge, few studies have assessed the serum level of SIRT1 in patients with CAD [11, 12].

The present study aimed to measure the plasma levels of SIRT1 in CAD patients and to explore its relationship with cardiovascular risk factors.

Our results showed that plasma SIRT1 levels were significantly lower in the UA and AMI groups than in the CCS and control groups. However, the difference between the AMI and CCS groups was not statistically significant, while the plasma SIRT1 level was significantly lower in the CCS group than in the control group. Similar to our results, Doulamis et al. [11] reported a significantly low level of serum SIRT1 in patients with advanced CAD. Moreover, they noticed an increased prevalence of AMI in patients with low SIRT1 levels [11].

Another study by Mariani et al. [13] found that circulating SIRT1 is inversely correlated with epicardial fat thickness, which is a candidate marker of cardiac ischemia. The authors suggested that plasma SIRT1 measurement might provide additional information for risk assessment of CAD, especially in obese people [13]. Low plasma SIRT1 levels in CAD patients may be due to its consumption in preventing the hazards of cardiac ischemia.

Another study reported that the cardiomyocyte-specific deletion of the *SIRT1* gene sensitizes the myocardium to ischemia and reperfusion injury [14], which indicates that changes in SIRT1 may be a cause of cardiac ischemia.

Fry et al. [24] assessed the SIRT1 level in media other than plasma or serum in CAD patients. The authors found that vascular smooth muscle SIRT1 protects against aortic stiffness, which is a major risk factor for IHD [24].

Several studies have also reported that SIRT1 expression is reduced in the monocytes of patients with CAD, that the *SIRT1* gene plays a protective role against ACS and that the activation of SIRT1 function reverses atherosclerotic events [9, 23, 25].

Interestingly, Li et al. [26] reported that SIRT1 expression significantly correlates with inflammatory cytokine levels in patients with CAD but not with the severity of coronary lesions [26].

Yamac and Kilic [27] noticed a significant increase in SIRT1 levels and expression in CAD patients who received statin therapy and concluded that SIRT1 might have a cardioprotective role after AMI. However, Kilic et al. [28] previously reported (in 2015) that the protective effect of statin treatment on CVD is through the inhibition of SIRT1 expression.

The present study showed no significant correlation between SIRT1 with age. This can be explained by the limited age range of the participants selected. However,

few studies have assessed the negative correlation between SIRT1 and age [30, 31]. Engelfriet et al. [29] found that the SIRT1 level in blood lymphocytes might be a promising biochemical marker associated with aging [19].

In our study, there was a significant difference between serum urea and BUN levels between the study groups as they were significantly higher in the AMI group than in the other groups. In agreement with our findings, a prospective study carried out by Horiuchi et al. in 2018 found that BUN and serum urea levels were significantly higher in ACS patients and can be useful predictors of ACS [32].

We did not notice, however, a significant correlation between plasma SIRT1 levels and blood urea levels. This result is contrary to that obtained by Doulamis et al. [11], who reported a significant negative correlation [11].

In our study, serum total cholesterol, TG, and LDL were significantly lower, and HDL was significantly higher in the control group than in the CAD groups. In agreement with our results, Dobiasova and Frohlich [33] observed an inverse correlation between baseline HDL levels and both cardiovascular and all-cause death in the general population. Moreover, they found a significant inverse correlation of HDL with LDL particles, which are strongly correlated with the initiation and progression of atherosclerosis [33]. Moreover, Mendivil et al. [34] associated the risk contributed by LDL to the presence of apolipoprotein C-III [34].

In our study, there was a significant difference in CK-MB levels between the study groups. These levels were higher in the CAD group. Our results agree with those of Chan et al. [9], who found that creatine kinase, total cholesterol, and LDL concentrations were higher in CAD patients than in control subjects [9].

In our study, a significant positive correlation was found between plasma SIRT1 levels and platelet counts. This is similar to the results of Moscardó et al. [35]. The authors demonstrated that the inhibition of SIRT1 was associated with a concentration-dependent inhibition of the platelet responses, including platelet aggregation, dense granule secretion, and increase in cytosolic calcium levels, suggesting a regulatory role for SIRT1 in platelet responses.

In the present study, the plasma SIRT1 level was also found to be significantly negatively correlated with both cholesterol and TG. These results are congruent with those of Li et al. [36], who demonstrated that SIRT1 activates liver X receptors (LXRs), which in turn regulate the transfer of cholesterol from peripheral tissues to the liver (reverse cholesterol transport), thereby regulating cholesterol homeostasis [36].

Differences between our results and those of other studies may be explained by differences in ethnicity, lifestyle, and characteristics of the patients included.

5 Conclusions

Our results demonstrated that the plasma levels of SIRT1 were lower in CAD patients compared to normal control. Besides, there was a significant positive correlation between plasma SIRT1 and platelet count and a significant negative correlation between plasma SIRT1 and both cholesterol and TG. We predicted that low SIRT1 could be a new risk factor for CAD and SIRT1 activation could be a possible preventive factor of CAD. However, this needs to be validated by further molecular studies with multi-center cooperation, different ethnic groups, and follow-up measurements.

Abbreviations

CAD: Coronary artery disease; SIRT1: Silent information regulator 1; CCS: Chronic coronary syndrome; AMI: Acute myocardial infarction; UA: Unstable angina; NAD: Nicotinamide adenine dinucleotide; CBC: Complete blood count; RBS: Random blood sugar; CK-MB: Creatine kinase-MB; PPV: Positive predictive value; NPV: Negative predictive value; CVD: Cardiovascular diseases; ROS: Reactive oxygen species.

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Authors' contributions

IE and AMA designed and directed the project. RMA, AAA, and SH performed the experiments and analyzed the data. AAA and SH wrote the manuscript. All authors have read and approved the manuscript.

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from the patients or their relatives with an explanation of the study procedure and possible associated hazards. The study was approved by Institution Review Board (IRB), Faculty of Medicine, Zagazig University (ZU-IRB# 3931/13-–2017).

Consent for publication

Not applicable.

Competing interests

The authors have no conflict of interest to declare.

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