Presence of Microvascular Dysfunction and CHA₂DS₂-VASc Score in Patients with ST-Segment Myocardial Infarction after Primary Percutaneous Coronary Intervention

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Keywords

Indexed microvascular resistance · ST-segment elevation myocardial infarction · CHA₂DS₂-VASc score

Abstract

Objective: We aimed to investigate the relation between CHA₂DS₂-VASc score and microvascular dysfunction (MVD) assessed by the index of microvascular resistance (IMR) immediately after primary percutaneous intervention (PPCI) for patients with ST-segment elevation myocardial infarction (STEMI). **Subjects and Methods:** The study included 115 consecutive patients with STEMI who underwent successful PPCI. Angiographic results of reperfusion were inspected to evaluate the association of high CHA₂DS₂-VASc score and IMR. Also, we assessed echocardiographic changes with respect to CHA₂DS₂-VASc score. **Results:** Subjects were stratified into 2 groups based on IMR $\leq$ 40 U; 72 patients (62.6) with IMR $<$ 40 U and 43 patients (37.4) with IMR $\geq$ 40 U. Patients with IMR $\geq$ 40 U had higher CHA₂DS₂-VASc score ($p < 0.001$). CHA₂DS₂-VASc score was significantly correlated with increased left atrial volume index, diastolic dysfunction, wall motion score index, and inversely correlated left ventricular ejection. Moreover, CHA₂DS₂-VASc score was strongly correlated with IMR ($p < 0.001$). At multivariate analysis, low sys-

tolic blood pressure, stent diameter, and CHA₂DS₂-VASc score were associated with MVD. Besides, CHA₂DS₂-VASc score ≥ 4 was the optimal value in predicting MVD (IMR ≥ 40) in STEMI patients. **Conclusions:** The data of the current study point out that increased CHA₂DS₂-VASc score, lower systolic blood pressure < 90 mm Hg, and stent diameter are associated with increased incidence of MVD (increased IMR) after PPCI of STEMI. We suggest that the CHA₂DS₂-VASc score may be a simple, inexpensive useful risk score for the prediction of MVD risk after PPCI for STEMI patients.

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Introduction

Reducing the mortality of myocardial infarction depends largely on early diagnosis and effective treatment. Early active initiation of effective coronary reperfusion therapy is an important part of the treatment of myocardial infarction. The most serious form of acute coronary syndrome is ST-segment elevation myocardial infarction (STEMI) [1]. Currently, primary percutaneous coronary intervention (PPCI) is the preferred choice for the treatment of STEMI. This can reduce the mortality of acute myocardial infarction [2]. However, the presence of im-

paired microvascular function immediately following PPCI, as assessed by index of microcirculatory resistance (IMR), correlates with peak CK levels at presentation, left ventricular function at 3 months, and functional recovery at 3 months based on wall motion score and myocardial salvage [3, 4]. Fearon et al. [5] have demonstrated that IMR is an independent, reproducible, and quantitative invasive parameter of microvascular function, regardless of epicardial disease and hemodynamic perturbations.

The CHA₂DS₂-VASc score (congestive HF, hypertension, age ≥ 75 years [doubled], diabetes mellitus, prior stroke or transient ischemic attack [doubled], and vascular disease, age 65–74 years, and sex category [female]) was developed from the CHA₂DS₂ score and has been used extensively to predict thromboembolic events in patients with nonvalvular atrial fibrillation and determine whether to use anticoagulant or antiplatelet drugs [6].

We sought to investigate the presence of microvascular dysfunction (MVD) and clinical usefulness of CHA₂DS₂-VASc score for predicting MVD assessed by IMR in patients with acute myocardial infarction who underwent PPCI.

Subjects and Methods

One hundred and fifteen consecutive patients presenting with first acute STEMI who underwent PPCI between December 2018 and February 2020 were enrolled. In brief, the diagnosis of STEMI was made throughout the criteria of typical symptoms of myocardial ischemia (long-lasting chest pain >30 min), detection of >1 mm ST-segment elevation in at least two contiguous ECG leads, and elevated cardiac biomarkers, as defined by recommendation of the American College of Cardiology and the European Society of Cardiology guidelines [7].

The demographic variables, medical histories, and clinical features of all patients were taken. The CHA₂DS₂-VASc score of each patient was calculated. As all of the patients underwent a PPCI, each patient had a CHA₂DS₂-VASc score of at least 1.

The CHA₂DS₂-VASc score was the sum of one point each for the presence of congestive heart failure, hypertension, diabetes mellitus, age of 65–74 years, female sex, and vascular diseases (history of MI, peripheral arterial disease (PAD), or complex aortic plaques) and two points for age ≥ 75 years and a history of stroke or transient ischemic attack [8]. PAD was defined as the documentation of 50% stenosis in noncoronary arteries. Chronic renal failure was based on a creatinine clearance of <60 mL/min, which was calculated using the Cockcroft formula [9].

Patients with non-STEMIs, left or right bundle branch block, pacing, significant arrhythmias, and hemodynamic instability (shock) were excluded from the study. The study protocol was approved by the local Ethics Committee, and the study was carried out according to the principles of the Declaration of Helsinki. All participants gave an informed consent.

Evaluation of IMR

Microvascular function was evaluated in every patient after successful PPCI by measuring IMR as previously described with the temperature- and pressure-sensing guide wire [10, 11]. In brief, IMR was assessed using a coronary pressure/temperature sensor-tipped guide wire placed distally in the culprit lesion. A 2-mL intracoronary bolus of 200 μ g nitrate, followed by 140 μ g/kg/min of intravenous adenosine was used to induce hyperemia. Then, we recorded the mean aortic and distal coronary pressures during maximal hyperemia. The formula of distal coronary pressure multiplied by the mean transit time of a 3-mL bolus of saline at room temperature during maximal coronary hyperemia (mm Hg·s or U) was used to calculate IMR. $IMR = Pd_{Hyp} \times Tmn_{Hyp}$ (where Pd is the mean hyperemic distal pressure and Tmn_{Hyp} is the mean hyperemic transit time).

Echocardiographic Assessment

All participants underwent echocardiographic study to assess in-hospital cardiac changes. Echocardiographic images were taken with the use of a VIVID 7 echocardiographic system (GE Medical Systems, Princeton, NY, USA). The standard parasternal long and short axes, and apical four- and two-chamber views were obtained, and all measurements were in accordance with the American College of Cardiology for echocardiographic recommendations [12]. The following parameters were assessed: the regional wall motion score index (RWMSI), left ventricular ejection fraction (LVEF %) using the modified Simpson's rule, E/e' ratio, and left atrial volume index (LAVI).

Statistical Analysis

Kolmogorov-Smirnov statistic was performed to assess the data normality. Continuous data were expressed as mean $\pm$ standard deviation (SD). Distinct variables were presented as frequencies and percentages. Continuous variables were compared using Student's *t* test or using Mann-Whitney U test, based on the normality of data. χ^2 or Fisher's exact test were used to compare categorical variables. Pearson correlation coefficient test was used to find out the correlations between two continuous variables. Univariate and multivariate regression analyses were used to detect the predictors of MVD based on the cut-off value of $IMR \geq 40$ U as defined by Fearon et al. [13]. Variables in univariate analyses with $p < 0.1$ were entered into multivariate regression analysis. Receiver operating characteristic curve analysis was used as a measure of test accuracy. Data were analyzed using SPSS for Windows v.24 (SPSS, Chicago, IL, USA) statistical software package.

Results

A total of 115 patients with STEMI were enrolled for the study. All patients underwent IMR evaluation after PPCI to detect MVD. Based on the report by Fearon et al. [13] that states $IMR \geq 40$ was the optimal prognostic cut-off value of MVD in patients with STEMI, we stratified the study cohort into two groups, a group with MVD that included 43 patients (37.4%) with $IMR \geq 40$ and a group without MVD that included 72 patients (62.6%).

Table 1. Baseline characteristics based on index of microvascular resistance $\leq$ 40 units

	IMR $\leq$ 40 U (n = 72) (62.6%)	IMR $\geq$ 40 U (n = 43) (37.4%)	p value
Age, years	62.5 $\pm$ 8.5	69.9 $\pm$ 9.1	<0.01
Female sex, n (%)	28 (32.8)	23 (53.5)	<0.03
BMI	24.5 $\pm$ 0.9	25.3 $\pm$ 0.7	0.39
Smoking, n (%)	25 (34.7)	19 (44.1)	0.43
Hyperlipidemia, n (%)	31 (43)	20 (46.5)	0.66
Family history, n (%)	23 (31.9)	17 (39.5)	0.051
Hypertension, n (%)	31 (43.1)	20 (46.5)	0.35
Diabetes mellitus, n (%)	22 (30.5)	21 (48.8)	<0.03
History of heart failure, n (%)	0 (0)	0 (0)	–
History of stroke/TIA, n (%)	6 (8.3)	4 (9.3)	<0.49
Previous myocardial infarction, n (%)	0	0	–
Vascular disease, n (%)	21 (29.2)	17 (39.5)	<0.03
SBP, mm Hg	119 $\pm$ 12	91 $\pm$ 8	<0.01
DBP, mm Hg	76 $\pm$ 9	62 $\pm$ 9	0.16
Heart rate, beats/min	85 $\pm$ 11	93 $\pm$ 13	>0.05
Triglycerides, mmol/L	4.18 $\pm$ 1.03	5.21 $\pm$ 1.06	0.31
High-density lipoprotein-C, mmol/L	1.09 $\pm$ 0.21	1.08 $\pm$ 0.19	0.70
Low-density lipoprotein-C, mmol/L	2.85 $\pm$ 0.73	3.15 $\pm$ 0.58	0.46
Glucose, mmol/L	8.65 $\pm$ 0.05	9.17 $\pm$ 0.05	0.13
eGFR, mL/min/1.73 m ²	96.5 $\pm$ 39.5	89.6 $\pm$ 32.5	0.15
Peak troponin-I, ng/mL	51.3 $\pm$ 22.4	67.5 $\pm$ 29.5	<0.05
Peak CK-MB, IU/L	189.5 $\pm$ 106.1	275.8 $\pm$ 129.5	<0.03
Brain natriuretic peptide, pg/mL	319 $\pm$ 108	708 $\pm$ 159	<0.05
Symptom-onset-to-balloon time, h	6.15 $\pm$ 3.28	6.95 $\pm$ 3.52	0.22
CHA ₂ DS ₂ -VAsC score	1.53 $\pm$ 1.17	2.95 $\pm$ 1.35	<0.001
Left ventricular ejection fraction, %	56.5 $\pm$ 5.0	47.3 $\pm$ 3.9	<0.03
Regional wall motion score index	1.52 $\pm$ 0.23	1.93 $\pm$ 0.22	<0.01
Left atrial volume index, mL/m ²	25.6 $\pm$ 6.5	35.3 $\pm$ 10.0	<0.01
E/A ratio	1.01 $\pm$ 0.10	0.99 $\pm$ 0.10	0.23
E/e' ratio	7.3 $\pm$ 2.1	10.5 $\pm$ 2.5	0.03

BMI, body mass index; TIA, transient ischemic attack; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; cTnI, cardiac troponin; PPCI, primary percutaneous intervention; IMR, index of microcirculatory resistance.

Table 1 depicts the baseline and echocardiographic characteristics based on index of microvascular resistance $\leq$ 40 units. Compared with the patients without MVD, patients with MVD were older with a higher female percentage ($p < 0.001$ and $p < 0.03$, respectively). Furthermore, diabetes mellitus ($p < 0.03$) and vascular disease ($p < 0.03$) were common in patients with MVD compared with those without. Systolic blood pressure (SBP) was significantly lower in patients with MVD ($p < 0.01$). As regards laboratory data, the results showed that brain natriuretic peptide ($p < 0.05$), peak troponin-I ($p < 0.05$), and peak CK-MB ($p < 0.03$) were significantly higher in patients with MVD. The mean CHA₂DS₂-VAsC score was significantly higher in patients with MVD than in the patients without MVD (2.95 $\pm$ 1.35 vs. 1.53 $\pm$ 1.17; $p < 0.001$).

With respect to echocardiographic characteristics, patients with IMR $\geq$ 40 U had significantly increased LAVI ($p < 0.01$), increased E/e' ratio ($p < 0.03$), increased RWM-SI ($p < 0.01$), and a significant decrease in LVEF ($p < 0.03$), while, as shown, other baseline characteristics were comparable among both groups. Table 2 represents the angiographic characteristics of patients with IMR $\geq$ 40 U compared with those with IMR $\leq$ 40 U. As shown, the findings of the current study revealed that except for the stent diameter ($p < 0.03$), all angiographic data were comparable among both groups.

As observed in Table 3, correlation analysis revealed that the CHA₂DS₂-VAsC score was significantly correlated with RWMSI ($r = 0.51$; $p < 0.01$), LAVI ($r = 0.49$; $p < 0.01$), E/e' ratio ($r = 0.33$; $p < 0.05$), and IMR ($r = 0.63$;

Table 2. Angiographic characteristics according to IMR value

	IMR <40 U (n = 72)	IMR ≥40 U (n = 43)	p value
Culprit vessel, n (%)			
LAD lesion (66)	41 (56.9)	25 (58.1)	0.61
LCX (18)	10 (13.9)	8 (18.6)	0.59
RCA (31)	21 (29.2)	10 (23.3)	0.53
Pre-PPCI TIMI, n (%)			
0–1	49 (68.1)	31 (72.1)	0.71
≥2	23 (31.9)	12 (27.9)	0.71
Post-PPCI TIMI, n (%)			
2	14 (19.4)	13 (30.2)	0.19
3	58 (80.6)	30 (69.8)	0.19
Procedure data			
Mean stent diameter, mm	3.31±0.27	2.95±0.29	<0.03
Total stent length, mm	25.3±8.1	26.5±7.8	0.49
Direct stenting, n (%)	11 (15.3)	7 (16.3)	0.89
Aspiration thrombectomy, n (%)	61 (84.7)	36 (83.7)	0.91
Use of platelet glycoprotein IIb/IIIa inhibitors, n (%)	23 (31.9)	15 (34.9)	0.75

LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery; PPCI, primary percutaneous coronary intervention; IMR, index of microcirculatory resistance.

$p < 0.001$). On the other hand, it was inversely correlated with LVEF% ($r = -0.42$; $p < 0.01$).

Univariate logistic regression analysis showed that high CHA₂DS₂-VASc score, advanced age ≥75, lower SBP, low LVEF, increased LAVI, high-peak creatine kinase-myocardial band, and stent diameter were significant predictors of MVD after PPCI. At multivariate analysis, the results revealed that low SBP, stent diameter, and CHA₂DS₂-VASc score remained significant predictors for MVD after PPCI, with the strongest predictive value for CHA₂DS₂-VASc score ($p < 0.001$) (Table 4). Table 5 depicts the univariate and multivariate prediction of individual component and CHA₂DS₂-VASc score. As shown, the results revealed that age ≥75 years, diabetes mellitus, vascular disease, and CHA₂DS₂-VASc score were associated with MVD at univariate analysis, while at multivariate analysis, CHA₂DS₂-VASc score remained the strongest predictor for MVD.

By receiver operating characteristic curve analysis, CHA₂DS₂-VASc score ≥4 performed well for the detecting MVD assessed by IMR (IMR ≥40 U) with an area under the curve of 0.87 (0.80–0.95, $p < 0.001$) with a sensitivity of 86% and a specificity of 91% (Fig. 1). In spite of comparable TIMI flow values before and after PPCI, the results revealed that IMR was significantly increased in patients with CHA₂DS₂-VASc ≥4 ($p < 0.001$, Fig. 2).

Table 3. Correlations between CHA₂DS₂-VASc score and echocardiographic and IMR findings

	r	p value
Left ventricular ejection fraction, %	−0.42	<0.01
Regional wall motion score index	0.51	<0.01
Left atrial volume index, mL/m ²	0.49	<0.01
E/e' ratio	0.33	<0.05
IMR	0.63	<0.001

IMR, index of microcirculatory resistance.

Discussion

The current study has shown that a significant percentage (37.4%) of patients with STEMI had MVD. Furthermore, we found a significant relation between CHA₂DS₂-VASc score and MVD as assessed by IMR immediately after PPCI. In addition, CHA₂DS₂-VASc score was significantly correlated with increased LAVI, diastolic dysfunction, wall motion score index, and inversely correlated left ventricular ejection and. Besides, a CHA₂DS₂-VASc score ≥4 was the optimal value in predicting MVD (IMR ≥40) in STEMI patients, who underwent PPCI.

Table 4. Univariate and multivariate regression analysis of studied variables for predicting MVD after PPCI

	Univariate analysis odds ratio (95% CI)	<i>p</i> value	Multivariate analysis odds ratio (95% CI)	<i>p</i> value
Age ≥75 years	1.57 (1.06–2.91)	<0.03	1.42 (0.65–2.05)	0.11
SBP <90 mm Hg	1.95 (1.01–4.12)	<0.01	1.85 (0.95–3.65)	<0.05
LVEF	1.35 (1.02–1.49)	<0.05	0.92 (0.85–1.07)	0.57
LAVI	0.97 (0.92–1.08)	<0.03	0.88 (0.90–1.05)	0.38
Peak CK-MB	1.05 (1.00–1.09)	0.07	1.00 (0.91–1.02)	0.25
Stent diameter	1.15 (0.98–1.83)	<0.01	1.62 (1.05–2.18)	<0.03
Symptom-onset-to-balloon time	0.98 (0.81–1.47)	0.23	1.05 (0.14–0.45)	0.09
CHA ₂ DS ₂ -VASc score	1.9 (1.40–2.79)	<0.003	2.35 (1.45–3.25)	<0.001

SBP, systolic blood pressure; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index; CK-MB, creatine kinase-myocardial band; eGFR, estimated glomerular filtration rate; IMR, index of microcirculatory resistance; PPCI, primary percutaneous coronary intervention.

Table 5. Univariate and multivariate regression analyses of CHA₂DS₂-VASc score and its individual components for predicting high IMR (IMR ≥40)

	Univariate analysis HR (95% CI)	<i>p</i> value	Multivariate analysis HR (95% CI)	<i>p</i> value
Age ≥75 years	1.92 (1.08–3.70)	<0.01	1.65 (1.08–3.15)	<0.05
Age 65–74 years	1.06 (0.83–1.35)	0.46		
Gender female	0.98 (0.21–3.19)	0.52		
Hypertension	1.07 (0.95–1.18)	0.26		
Diabetes mellitus	1.82 (1.13–4.09)	<0.01	1.50 (0.93–3.38)	<0.05
Prior stroke/TIA	1.33 (0.91–4.55)	0.32		
Vascular disease	2.26 (0.99–9.13)	<0.02	1.45 (1.03–2.94)	0.17
CHA ₂ DS ₂ -VASc score	3.85 (1.57–5.81)	<0.001	3.45 (1.92–5.33)	<0.001

IMR, index of microcirculatory resistance; TIA, transient ischemic attack.

It is important to identify MVD, as STEMI patients with MVD are at high risk for heart failure and delayed functional recovery, larger infarct size, and unfavorable clinical events [14, 15]. According to the guidelines, the main propose for the development and validation of the CHA₂DS₂-VASc score was to assess the thromboembolic risks in subjects with nonvalvular atrial fibrillation [16]. Nonetheless, the components of the CHA₂DS₂-VASc score, for example, hypertension, diabetes mellitus, and age are considered main risk factors for cardiovascular atherosclerosis. For that, many previous studies supposed that the CHA₂DS₂-VASc score could be a predictor of the severity of coronary artery disease [17, 18].

Several investigators have studied the clinical utility and significance CHA₂DS₂-VASc score in a variety of clinical problems. These studies demonstrated that the CHA₂DS₂-VASc risk score was an independent predictor

of no reflow in patients with STEMI and increased in-hospital and long-term adverse events in patients with acute coronary syndrome [19–23]. Consistent with these findings, hypertension, diabetes mellitus, female sex, and aortic atherosclerosis, which constitute the chief components of the CHA₂DS₂-VASc score, are associated with MVD [24]. These findings might provide the significance of the score in prediction and prognosis of MVD in STEMI patients after PPCI.

The components of the CHA₂DS₂-VASc score are important risk factors of cardiovascular atherosclerosis and MVD [25, 26]. But, when we performed multivariate analysis for individual components of the CHA₂DS₂-VASc score, we found that the CHA₂DS₂-VASc score had the strongest predictive value for MVD in STEMI patients after PPCI.

Fig. 1. In terms of the detection of MVD (IMR ≥ 40 U) after the PPCI, the CHA₂DS₂-VASc score had an area under the curve of 0.87 (0.80–0.95, $p < 0.001$) on the ROC curve. The ROC analysis showed that the best cut-off value of the CHA₂DS₂-VASc score to predict acute stent thrombosis was ≥ 4 , with 86% sensitivity and 95% specificity. MVD, microvascular dysfunction; IMR, index of microcirculatory resistance; PPCI, primary percutaneous coronary intervention; ROC, receiver operating characteristic.

We supposed that MVD may be associated with increased CHA₂DS₂-VASc score. The pathophysiologic link is variable. Our study showed that IMR was significantly higher in patients with a high CHA₂DS₂-VASc score. In addition, patients with higher IMR had a significant increase in LAVI, increased E/e' ratio and lowered LVEF%.

Many researchers have described the capability of IMR to predict left ventricular functional recovery at 3 months, either after primary coronary intervention or rescue coronary intervention [27–29]. Ischemia may happen, despite successful revascularization and restoring blood flow in the coronary arteries as a result of MVD [30]. It is widely accepted that TIMI flow grade and myocardial blush grade are a good semiquantitative assessment of microvascular perfusion; yet, several studies reported that alone, successful angiographic revascularization does not reliably predict the incident of impaired microvascular function [31, 32]. Furthermore, Fearon et al. [33] reported that a mean IMR value ≥ 40 U after PPCI for STEMI patients had a significantly higher rate of mortality and adverse outcomes at 1 year than in STEMI pa-

Fig. 2. The IMR after PPCI in patients with STEMI based on the CHA₂DS₂-VASc score. IMR was higher in patients with CHA₂DS₂-VASc score ≥ 4 ($p < 0.001$). IMR, index of microcirculatory resistance; PPCI, primary percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

tients, who had an IMR ≤ 40 U. They demonstrated that an IMR ≥ 40 U was an independent risk factor for mortality and heart failure during long-term follow-up and death alone, whereas TPMG and CTFC were not predictors for these adverse events [33].

The results of the current study revealed that lower SBP was significantly associated with the presence of MVD. This could be linked to reduction of perfusion pressure of coronary arteries as a result of lower blood pressure. In addition, oxidative stresses of endothelial cells result in vasoconstriction and consequently lead to reduction of coronary microvasculature [34]. Furthermore, microvasculature bed might be compressed by swelled myocardial cells and interstitial edema [35].

Some of the components of the CHA₂DS₂-VASc score, including advanced age, diabetes mellitus, female sex, hypertension, and heart failure, are linked to MVD [36–38]. Accordingly, overlapping of risk factors and collective pathophysiologic mechanisms might deduce the clinical usefulness of the CHA₂DS₂-VASc score in prediction of MVD. Moreover, usage of CHA₂DS₂-VASc score is a simple and a quick predictor of MVD in STEMI patients before PPCI.

Limitations of This Study

The raised limitations were as follows: first, this was an observational, single-center study and second, selection bias, which may affect the statistical results, even though we recruited consecutive patients.

Clinical Implication

ST-segment myocardial infarction is a serious clinical situation that requires urgent revascularization. Nonetheless, MVD following PPCI may lead to adverse remodeling and unfavorable short- and long-term outcomes. Being a simple, inexpensive, and non-laboratory-dependent risk score, the CHA₂DS₂-VAsC score may be a useful risk score for the evaluation of MVD risk after PPCI for STEMI patients and affords an opportunity for aggressive medical treatment.

Conclusion

The data of the current study point out that increased CHA₂DS₂-VAsC score, lower SBP <90 mm Hg, and stent diameter are associated with increased incidence of MVD (increased IMR) after PPCI for STEMI patients. Furthermore, we found that CHA₂DS₂-VAsC score of ≥ 4 had a strong predictive value to identify patients at risk of MVD after PPCI.

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Statement of Ethics

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later revisions. Informed consent was obtained from all patients for being included in the study. 653-2018. All participants gave an informed written consent and the study protocol was approved by the faculty Ethical Committee.

Conflict of Interest Statement

Authors declare that they have no conflict of interest.

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Author Contributions

Ragab A. Mahfouz is the corresponding author, perceived the idea, designed the work, and wrote and submitted the manuscript. Marwa Gad contributed to the analysis and interpretation of data and shared in writing the paper. Moei Eldeen AbulFotouh and Mohamed Arab contributed to data collection, analysis of data, and writing and drafting the paper and revised it critically.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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