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Prediction of Failed Coronary Reperfusion after Thrombolytic Therapy in ST - Segment Elevation Myocardial Infarction Patients.

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ABSTRACT

Background: Around the globe, acute myocardial infarction is the primary cause of congestive heart failure and death.There is currently no rating system in place to predict thrombolytic failure in STEMI patients.The aim of the study was to demonstrate that CHA2DS2-VASc-HS scores would predict missing reperfusion in STEMI patients on thrombolytic therapy.

Patients and methods: This is a cross sectional prospective study conducted on 70 patients with ST-segment elevation myocardial infarction who were treated with streptokinase who were grouped into two groups. Group I: STEMI patients with successful thrombolysis (30 patients). Group II: STEMI Patients with failed thrombolysis (40 patients). The CHA2DS2-VASc-HSF score was formulated and Coronary angiography was performed .Gensini score estimation for relative severity of these lesions and compared to CHA2DS2-VASc-HSF score for achieving the aim of the study.

Results:There was a statistically significant difference between both group according to CHA2DS2-VASc-HSF and Gensini score There was strong positive correlation between CHA2DS2-VASc-HSF score and Gensini score. The cut-off value of CHA2DS2-VASc-HSF score that can predict failed thrombolytic therapy in STEMI patients was 4 (AUC= 0.93%, CI 95% ranged from, sensitivity=95 %, specificity= 76%)

Conclusion:This score may help doctors working in non-PCI hospitals determine the risk of failed reperfusion using a well-documented formula that takes into account a variety of risk factors related to the severity of CAD in STEMI patients.

Keywords: ***CHA_2DS_2-VASc-HSF Score, Failed Coronary Reperfusion, ST-Segment Elevation Myocardial Infarction***

Introduction:

Acute myocardial infarction (AMI) is the leading cause of congestive heart failure and death around the world (**1,2,3**). The aim of the initial treatment plan in ST-segment

elevation myocardial infarction (STEMI) was to revascularize the culprit coronary artery as soon as possible **(4,5).**

Currently, there is no scoring scheme for predicting thrombolytic failure in STEMI patients. The CHA2DS2-VASc score is widely used to stratify thromboembolic risk in patients with atrial fibrillation (AF) **(6).**

The CHADS2 and CHA2DS2 -VASc scores are often used in clinical practise and provide related risk factors for coronary artery disease growth **(7).**

These ratings have been shown to have predictive validity in predicting the likelihood of death after a stroke. In addition to the previous CAD risk factors of asthma, diabetes mellitus, old age, and heart disease, a new score CHA2DS2-VASc-HSF was developed to include more variables such as hyperlipidemia (H), smoking (S), and family history of CAD (F) **(6)**

Both patients undergoing coronary angiography (CAG) had their scores assessed as multivariable risk evaluation instruments to ascertain the seriousness of CAD **(8).**

The study's aim was to show that CHA2DS2-VASc-HS scores are useful in forecasting missed reperfusion in STEMI patients receiving thrombolytic therapy.

Patients and Method:

This is a cross sectional prospective study conducted in the period from August 2019 to February 2020 in our tertiary care unit, department of Cardiology, Zagazig University where 70 patients with ST-segment elevation myocardial infarction who were treated with streptokinase who were grouped into two groups. Group I: STEMI patients with successful thrombolysis (30 patients). Group II: STEMI Patients with failed thrombolysis (40 patients).

Before prospective collection of patient data and after informed consent was received from patients, the study was carried out in conjunction with the World Medical Association (Declaration of Helsinki) for trials involving humans.

Inclusion criteria was patients diagnosed as ST-elevation myocardial infarction and candidate for thrombolytic therapy.

Exclusion criteria was severe renal or liver disease, infectious or inflammatory diseas, -previous or current neoplasm, -hematological disorder, patients who underwent primary percutaneous coronary intervention (ppci), or patients not candidate for thrombolytic therapy (contraindication for thrombolytic therapy)

Twelve lead ECGs were obtained for each patient at rest: with 10 mm/mV amplitude and 25 mm/sec rate with standard lead positions at 0, 1.5, 6, 12 hours after admission.

Diagnosis of STEMI by estimation of prolonged new convex ST-segment elevation, particularly when associated with reciprocal ST-segment depression, usually reflects acute coronary occlusion and results in myocardial injury with necrosis. Reciprocal changes can help to differentiate STEMI from pericarditis or early repolarization changes. Some of the earlier manifestations of myocardial ischaemia are typical T wave and ST-segment changes.

Increased hyper acute T wave amplitude, with prominent symmetrical T waves in at least two contiguous leads, is an early sign that may precede the elevation

of the ST-segment. The J-point (junction between QRS termination and ST-segment onset) is used to determine the magnitude of the ST-segment shift with the onset of the QRS serving as the reference point.

In patients with a stable baseline, the TP segment (isoelectric interval) is a more accurate method to assess the magnitude of ST-segment shift, and in distinguishing pericarditis (PTa depression) from acute myocardial ischaemia.

Tachycardia and baseline shift are common in the acute setting and can make this determination difficult. Therefore, QRS onset is recommended as the reference point for J-point determination.

New or presumed new, J-point elevation ≥1 mm (1 mm = 0.1 mV) is required in all leads other than V2 and V3 as an ischaemic response. In healthy men under age 40, J-point elevation can be as much as 2.5 mm in leads V2 or V3, but it decreases with increasing age. Sex differences require different cut-off points for women, since J-point elevation in healthy women in leads V2 and V3 is less than in men. For example, ≥ 2 mm of ST-elevation in lead V2 and ≥ 1 mm in lead V1 would meet the criteria of two abnormal contiguous leads in a man ≥40 years old. However, ≥ 1 mm and < 2 mm of ST-elevation, seen only in leads V2–V3 in men (or < 1.5 mmin women), may represent a normal finding **(8)**.

Streptokinase infusion was given as per protocol at the standard dose of 1.5 MU over 30-60 min. Failed thrombolysis was defined according to ECG criteria when less than 50% ST-segment resolution within 90 min from the initiation of the thrombolytic therapy.

The CHA2DS2-VASc-HSF score was formulated [heart failure (signs/symptoms of heart failure confirmed with objective evidence of cardiac dysfunction), hypertension (HT) (defined as measurements of systolic and diastolic blood pressure ≥ 140/90 mm Hg or taking antihypertensive medications), age, diabetes mellitus (DM) (defined as a fasting blood glucose level > 126 mg/dL or blood glucose ≥ 200 mg/dL or using anti diabetic drugs), previous ischemic stroke or transient ischemic attack (TIA), vascular disease(defined as myocardial infarction [MI] and peripheral artery disease including prior revascularization, amputation or angiographic evidence or aortic plaque), male sex, hyperlipidemia (defined as increased level of low density lipoprotein cholesterol (LDL-C) according to the National Cholesterol Education Program-3 recommendations and history of using lipid lowering medications), smoking status (defined as smoking > 10 cigarettes a day for at least one year without a quit attempt), and family history of CAD (defined as MI before 55 years of age for men or 65 years of age for women in first-degree relatives). Compared to the CHA2DS2 -VASc score, male gender instead of female as sex category, hyperlipidemia, smoking, And family history of CAD was added in this score) **(8)**

Coronary angiography was performed in Zagazig University Hospitals Catheterization laboratories (Cine angiographic equipment: GE Innova 2100- IQ**:** cine frame: 30 fps).Selective coronary angiography with standard multi-angulated angiographic views was performed through the femoral artery under local anesthesia

(2% Lidocaine) using the Judkins catheters and iopromide (Ultravist) as the contrast agent. The angiograms were recorded on a compact disc in DICOM format.

Gensini score estimation for relative severity of these lesions using a score of 1 for 25 % obstruction and doubling that number as the severity of the obstructions progresses according to the indicated reduction of lumen diameter (left column).

Statistical analysis

Results were tabulated and statistically analysedusing IBM SPSS software package version 20.0(Armonk, NY: IBM Corp). In all tests, P value below 0.05 was considered statistically significant.

Results:

The age ranged from 38 to 74 years old (56±18), with 8 of them (26.6%) was between 65-74 years old in Group I, while in Group II, it ranged from 49 to 76 years old (62.5±13.5), with 3 of them(7.5%) above 75 years old and 22 (55%) ranged between 65-74 years old. Statistically, this difference was very highly significant (p<0.001).There was statistically significant difference between the studied groups regarding age, hypertension, diabetes mellitus and dyslipidemia (p value <0.05), but there was no significant difference between the study groups regarding smoking, gender and family history of premature CAD (p value >0.05) **(Table 1).**

There was highly significant difference between the studied groups regarding EF p value < 0.05 **(Figure 1)**. There was highly significant difference regarding serum level of total cholesterol and HDL with p value <0.001, but there was statistically non-significant difference between the studied groups regarding serum level of Triglycerides and LDL with p value >0.05 **(Table 2).**

Table (1): Demographic data and risk factors of the study groups.

Variable	Group (I) (n=30)		Group (II) (n=40)		Χ2	Significance
	No.=30	Percentage	No.=40	percentage	Χ2	p-value
Age (65-74 years old)	8	26.6%	22	55%	14.339	0.00077***
(≥75 years old)	-	-	3	7.5%		
Gender (M)	23	76.6%	29	72.5%	0.014	0.91
HTN	15	50%	31	77.5%	4.6	0.032*
DM	13	43.3%	32	80%	8.505	*0.00354**
Smoking	14	46.6	28	70%	2.9774	*0.08*
+ve family history of premature CAD	6	20%	15	37.5%	1.7361	0.188
Dyslipidemia	7	23.3%	24	60%	7.9141	0.0049*

M: Male, CAD: coronary artery disease, HTN: Hypertension, DM: diabetes, χ^2=mean, *: significant, ***: very highly significant.

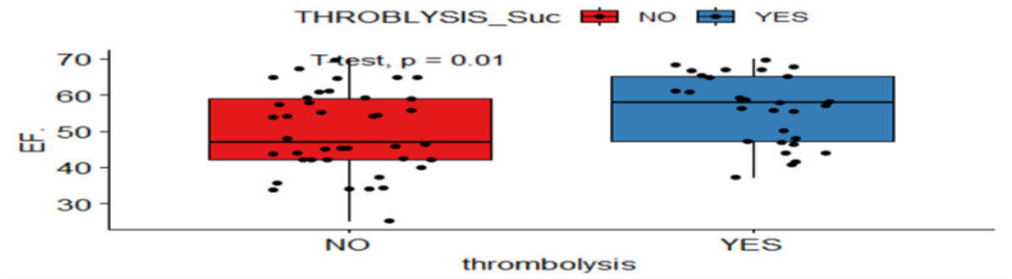

Figure (1): Comparison of EF between both groups

Table (2): Serum lipids variables between the studied groups.

Variable	Group I		Group II		t-value	significance
	Mean	SD	Mean	SD	t-value	p-value
Total cholesterol (mg/dl)	182.35	27.8	207.76	31.4	3.6	0.00066**
Triglycerides (mg/dl)	138.2	22.94	147.25	26.24	1.54	0.13
HDL (mg/dl)	29.6	3.2	33.34	4.37	4.14	0.0001**
LDL (mg/dl)	109.44	25	112.65	23.34	0.5	0.6

**: highly significant. HDL: high density lipoprotein, LDL: low density lipoprotein.

According to CHA2DS2-VASc-HSF value and statistical analysis between the studied groups, it was 2.9±1 ranged from 2-6 in Group I, while in group II it was 5.23±0.95 ranged from 3-7. Statistically this difference was very highly significant (t=9.4, p <0.001). According to Gensini score value and statistical analysis between the study groups, it was 60.5±25 ranged from 40 to 156 in Group I, while in group II it was 80.2±21.7 ranged from 43 to 145. Statistically significant (t=3.5, p <0.05) **(Table 3)**.

There was strong positive correlation between CHA2DS2-VASc-HSF score and Gensini score, statistically significant p value <0.05 **(Fig. 2)**.

A ROC analysis was performed. The cut-off value of CHA2DS2-VASc-HSF score that can predict failed thrombolytic therapy in STEMI patients was 4 (AUC= 0.93%, CI 95% ranged from, sensitivity=95 %, specificity= 76%) **(Fig. 3).**

Table (3): CHA2DS2-VASc-HSFand Gensini value between the studied groups.

Variable	Successful thrombolysis (Group I)		Failed thrombolysis (Group II)		t-value	Significance
	Mean	SD	Mean	SD	t-value	P-value

CHA2DS2-VASc-HSF	2.9	1	5.23	0.95	9.4	0.0000000000002224*
Gensiniscore	60.5	25	80.2	21.7	3.5	0.0011**

** Highly significant* *** significant*

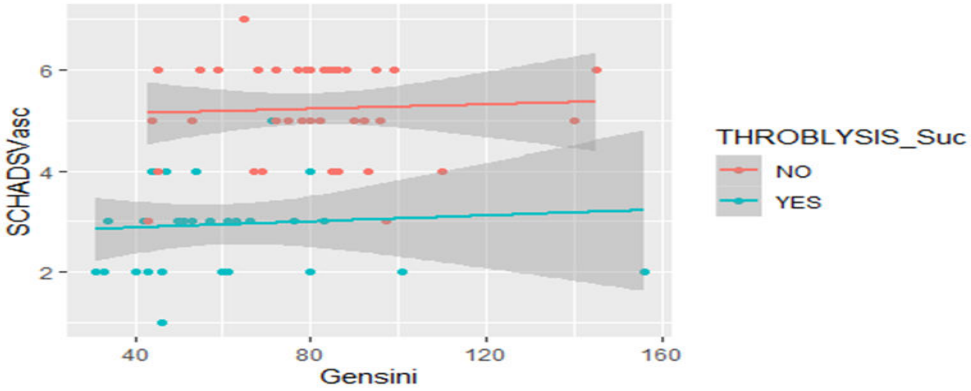

Figure (2) show statistically significant strong positive correlation between CHA2DS2-VASc-HSF score and Gensini score.

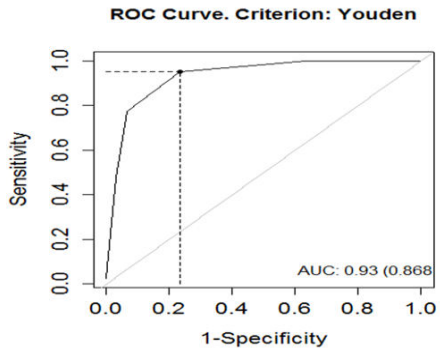

Figure (3) receiver–operating characteristics analysis curves (ROC curve) showing the cutoff values of CHA2DS2VASc-HS scores for failed thrombolysis in patients with STEMI

Discussion:

Reperfusion fails in almost one third of patients receiving thrombolytic therapy, and these patients require a rescue PCI (**11,12**). The CHADS2 and CHA2DS2-VASc scores are clinical predictors used to evaluate the risk of cardiac thromboembolism and to guide antithrombotic therapy (**13**). Furthermore, their components are (hypertension, diabetes mellitus, old age, and heart failure) which were also shown to be risk factors for poor clinical outcomes in cardiovascular diseases.

Recently, CHADS2, CHA2DS2-VASc and newly defined CHA2DS2-VASc-HSF scores were tested to predict CAD severity using the Gensini score in patients who undergo diagnostic coronary angiography (**14**). In CHA2DS2-VASc-HSF score, the authors replaced the female gender with male gender, and they also incorporated

Hyperlipidemia & Smoking and Family history as risk factors for the development of CAD.

The present study demonstrated the value of the newly defined CHA2DS2-VASc-HSF scores in predicting reperfusion failure in STEMI patients treated with thrombolytic therapy and proposed a cut off value for rapid transfer of STEMI patients to PCI capable centers as early as possible.

The present study showed that there is highly statistically significant difference between the two groups regarding the age. the current study showed that failed thrombolytic therapy was more common among the age group between 65-74 years old with less percentage in the age group ≥75 years old and this goes with the fact that the elderly patients are frequently develop acute infarction in the setting of previous complications from ischemic heart disease and have an extremely high hospital mortality rate. The absence of chest pain on admission, nonspecific ECG abnormalities and presence of other comorbidities hampered the decision of treatment especially in ≥75 year's old age group, this low eligibility for thrombolytic therapy in this age group was a cause for stoppage trial which was designed for treatment of that age group **(15)**. **Weaver, et al., (16)** approved the same results ,unlikely **Krumholz, et al., (17)** found that usage of streptokinase in age ≥75 years old is beneficial and coast effective treatment.

In the present study the current study showed that there was no statistically difference between two groups in terms of gender distribution with high percentage of male affection in both groups this was concordant with kilic study which was performed with low proportion of female patients whom presented with STEMI and was eligible for thrombolytic therapy, and this limit the ability to demonstrate the potential impact of gender on reperfusion failure **Kilic, et al.,(18)**.However, **Woodfield, et al., (19)** found that there was no significant difference between male and female as regarding early infarction associated patency and reocclusion following thrombolytic therapy. Lower reperfusion rates in women, as compared to men, have been reported in many studies **(Bangalore et al., (20) ; Puymirat, et al., (21) and Khera et al., (22)** and this gap continues to persist and this may be attributed to the atypical presentation leading to delayed presentation or may be due to presence of a higher frequency of alternative etiologies (e.g., spontaneous coronary dissection, coronary vasospasm), and different angiographic findings **(22)**.

In the present study, cardiac risk factors which belongs to CHA_2DS_2-VASc-HSF score were presented with statistically significant difference between the studied groups regarding hypertension, diabetes mellitus and dyslipidemia (p value<0.05),unlike **Saleem, et al., (23)** which found that dyslipidemia has no statistically significant difference regarding to thrombolytic response in STEMI patients, also **Vennila and Karthik, (24)** found that hypertension have no influence on thrombolysis outcome, **Kilic et al., (25)** showed that hypertension more common among failed thrombolytic group and this goes with the fact that high BP is a major risk factor for CAD.

This can be explained by the production of fatty acid intermediates in diabetic patients which in turn promote ischemic injury through several mechanisms including

direct toxicity, increased oxygen demand, direct inhibition of glucose oxidation, and subsequent production of free radicals which lead to loss of integrity of membrane and eventually cell death. The high thrombolytic failure rate among diabetic patients may be attributed to the wide range of small vessels affection or due to late presentation in absence of chest pain sensation.

The current study showed that there was statistically non-significant difference between the studied groups regarding history of congestive heart failure, stroke/TIA and peripheral vascular disease (p value > 0.05).Unlike **Kilic et al., (25)** which found that presence of history of CHF can predict failed thrombolytic therapy in STEMI patients, but history of stroke/TIA couldn't be studied due to absence of STEMI presented patients with history of stroke/TIA. Also **Uysal, et al., (8)** found that the presence of previous history of CHF, stroke or vascular disease is associated with high atherosclerotic burden and sever coronary artery disease. This discordance can be explained by smaller number of patients with risky clinical history (CHF, stroke, vascular disease) in our studied groups whom mainly treated with PPCI strategy under our staff recommendations.

Throughout the present studythe current study showed that inferior wall myocardial infarction (IWMI) mainly associated with higher rate of successful thrombolysis compared to anterior wall myocardial infarction (AWMI) with statistically significant difference between the studied groups. The current study showed that there was statistically non-significant difference between the studied groups regarding EDV, ESV p value > 0.05 but there was significant difference between the studied groups regarding EF p value <0.05. This was concordant with **Masoomi, et al., (26)** which found that failure of ST-segment resolution 180 min after streptokinase infusion is associated with lower ejection fraction and this goes with the fact that early thrombolysis in acute myocardial infarction help in preservation of global and regional left ventricular function **Serruys, et al., (27)**.

The current study showed that there was highly statistically difference between the studied groups regarding serum level of total cholesterol &HDL but there was non-significant statistical difference regarding triglycerides &LDL levels. This was discordant with **Kilic et al., (25)** which found that LDL of high significant unlike triglycerides which had non-significant statistical difference between the studied groups.

The current study showed thatCHA2DS2-VASc-HS score being of higher value in predicting failed reperfusion with a cut off value=4 (AUC= 0.93%, CI 95% ranged from, sensitivity=95 %, specificity= 76%) with significant correlation between CHA2DS2-VASc-HS and Gensini score. This was in cordance with **Kilic et al., (25)** which underlined the significance of the CHA2DS2-VASc and especially CHA2DS2-VASc-HSF scores as predictors of failed reperfusion after thrombolytic therapy in STEMI patients. **Cetin et al., (13)** investigated patients who underwent diagnostic angiography and found that CHADS2, CHA2DS2-VASc and CHA2DS2-VASc-HS scores were significantly correlated with the number of diseased coronary vessels and the Gensini score.

This study recommended that this new score should be validated in prediction of thrombolytic failure in STEMI patients with high score (cut off value=4). The CHA2-DS2-VASc-HSF score can be studied on a multi-center basis with follow up data such as in hospital or 30-day mortality and complications that could provide more information on prognostic value of CHA_2DS_2-VASc-HSF score in further studies.

One of the major limitations of this study is that it was a single-center study with small sample size and no follow-up data such as in hospital or 30-day mortality and complications that could provide more information on prognostic value of CHA_2DS_2-VASc-HSF score. Also the absence of patients with a history of ischemic or hemorrhagic stroke represents another major limitation. Nevertheless, stroke was not excluded from the scoring systems in order to guide future studies and avoid contravening the generic scoring systems. Usage of streptokinase as a thrombolytic drug add anew limitation as it is not as effective as the new generations of the tissue plasminogen activators (tPA) (e.g. alteplase and reteplase). Streptokinase has a limited fibrinolytic action as a result of "plasminogen steal" phenomena associated with its fibrin nonspecific property, accounting partly for the thrombolysis failure.

Conclusion

CHA2DS2VASc-HSF score can be useful in predicting failed reperfusion before thrombolytic therapy. This score can also enable doctors who work in non-capable PCI hospitals to assess the risk of failed reperfusion by using a well-recorded formula which includes a number of risk factors related to the severity of the CAD in STEMI patients. The formula is simple, quick and useful.

Conflict of Interest: No conflict of interest.

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